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Avaliação da importância da psoríase em placas moderada a grave como factor de risco cardiovascular: estudo numa população portuguesa

Tese de candidatura ao grau de Doutor em Ciências Médicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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1. Torres T, Alexandre JM, Mendonça D, Vasconcelos C, Silva BM, Selores M. ***Levels of Physical Activity in Patients with Severe Psoriasis: A Cross-Sectional Questionnaire Study.*** Am J Clin Dermatol. 2014 Apr;15(2):129-35.
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9. Torres T, Bettencourt N, Ferreira J, Carvalho C, Mendonça D, Pinho-Costa P, Vasconcelos C, Selores M, Silva B. ***Lack of association between leptin, leptin receptor and adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat and atherosclerotic burden in psoriasis patients.*** (submetido)

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2. Torres T, Bettencourt N. ***Psoriasis: The visible killer.*** Rev Port Cardiol. 2014 Feb;33(2):95-9.
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4. Sales R, Torres T. ***Psoriasis and metabolic syndrome.*** Acta Dermatovenerol Croat. 2014.
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5. Correia B, Torres T. ***Obesity: a key component of psoriasis***. (submetido)

ABREVIATURAS

AVC	Acidente vascular cerebral
BSA	*Body Surface Area*
CAC	Calcificação arterial coronária
CCL20	*Chemokine ligand 20*
CXCL10	*Chemokine ligand 10*
CI	*Confidence interval*
C3	Componente C3 do sistema de complemento
DLQI	*Dermatology Life Quality Index*
EAM	Enfarte agudo do miocárdio
FRCV	Factores de risco cardiovasculares
FRS	*Framingham risk score*
HLA	*Human Leukocyte Antigen*
HR	*Hazard-ratio*
HTA	Hipertensão arterial
IL-1	Interleucina 1
IL-6	Interleucina 6
IL-8	Interleucina 8
IL-10	Interleucina 10
IL-12	Interleucina 12
IL-17	Interleucina 17
IL-22	Interleucina 22

IL-23 Interleucina 23

IMC Índice de massa corporal

INF-α Interferão alfa

INF-γ Interferão gama

MCP-1 *Monocyte chemotactic protein 1*

NK *Natural killer*

OR *Odds-ratio*

PASI *Psoriasis Area Severity Index*

PCR Proteína C-reactiva

RR *Relative-risk*

SNP *Single-nucleotide polymorphism*

TCMD Tomografia computorizada multidetectores

TGF-β *Transforming growth factor beta*

Th1 *T helper 1 cells*

Th17 *T helper 17 cells*

Th22 *T helper 22 cells*

Treg *Regulatory T cells*

TNF-α Tumor necrosis factor alfa

VEGF *Vascular endothelial growth factor*

PREFÁCIO

Esta tese reúne os dados obtidos no âmbito do projecto de investigação intitulado "*Avaliação da importância da psoríase em placas moderada a grave como factor de risco cardiovascular: estudo numa população portuguesa*".

Encontra-se estruturada em 4 capítulos, precedidos por um resumo em Português e em Inglês.

O primeiro capítulo (Introdução) elabora uma introdução geral à tese. Inicia-se com uma revisão das manifestações clínicas e da fisiopatologia da psoríase. É, posteriormente, realizada uma revisão da evidência actual sobre a associação entre psoríase, comorbilidades cardiometabólicas e doença cardiovascular. Os objectivos da tese encontram-se, também, apresentados neste capítulo.

No segundo capítulo (Artigos Publicados) são apresentados os diversos artigos elaborados no âmbito desta tese. Referem-se, inicialmente, os artigos de revisão, seguido dos artigos originais que reúnem os resultados obtidos durante a investigação efectuada.

O terceiro capítulo (Discussão e Conclusão) inclui uma discussão sobre os estudos efectuados, organizada em 3 partes: 1) Influência de factores comportamentais e de abordagem médica dos doentes com psoríase no risco cardiovascular; 2) Marcadores de risco cardiovasculares em doentes com psoríase; 3) Influência de factores genéticos no desenvolvimento de doença cardiovascular na psoríase. Este capítulo encerra com uma conclusão sobre a investigação realizada.

Por fim, no quarto capítulo (Perspectivas Futura), apresentam-se alguns projectos já em desenvolvimento e potenciais linhas de investigação relacionadas com o tema desta tese.

RESUMO

A psoríase é uma doença inflamatória crónica que afecta 2 a 3% da população, associando-se a uma importante diminuição da qualidade de vida dos doentes e a um elevado impacto económico e social.

Nos últimos anos, a psoríase deixou de ser considerada uma doença exclusivamente cutânea. Actualmente considera-se uma doença inflamatória sistémica associada a diversas comorbilidades, em especial cardiometabólicas, tendo sido determinante a constatação de que os doentes com psoríase têm um risco superior de eventos cardiovasculares comparativamente com a população geral, com consequente aumento da mortalidade e uma diminuição da esperança média de vida em cerca de 5-6 anos. A prevalência aumentada de factores de risco cardiovasculares e a inflamação sistémica, presente especialmente nos doentes com psoríase grave, têm um papel essencial na aterosclerose precoce e acelerada observada nestes doentes. Contudo, os mecanismos responsáveis por esta associação não estão ainda totalmente esclarecidos, sendo provavelmente multifactoriais, envolvendo factores genéticos, imunológicos e ambientais. Adicionalmente, a identificação de marcadores laboratoriais e clínicos, que permitam reconhecer precocemente os doentes em maior risco de desenvolver doença cardiovascular é essencial e tem implicações práticas significativas, pois permitirá a adopção de medidas preventivas e terapêuticas nesses doentes.

O principal objectivo desta tese foi investigar marcadores clínicos e laboratoriais (genéticos e analíticos) que permitissem a identificação de doentes em risco de desenvolver comorbilidades cardiometabólicas e doença cardiovascular. O estudo da influência de polimorfismos genéticos no aumento do risco de doença cardiovascular em doentes com psoríase grave, especialmente de citocinas pró-inflamatórias e adipocinas conhecidas por participarem na fisiopatologia da psoríase, assim como das diversas comorbilidades cardiometabólicas e

aterosclerose, teve particular destaque neste projecto. Adicionalmente foram avaliados outros factores que pudessem ter influência no aumento do risco de doença cardiovascular nestes doentes, como factores comportamentais, factores associados à inflamação e marcadores de risco de doença cardiovascular recentemente identificados.

Neste contexto, demonstrámos que nos doentes com psoríase, além do risco cardiovascular intrínseco da doença, outros factores, nomeadamente comportamentais e associados ao estilo de vida e de abordagem médica destes doentes, contribuem para o aumento de risco cardiovascular. Assim, observámos que a actividade física e a proporção de doentes que cumpriam as recomendações para uma actividade física saudável estavam significativamente diminuídas nos doentes com psoríase comparativamente com o grupo controlo. Verificámos ainda, que a abordagem médica dos factores de risco cardiovasculares e da prevenção primária de eventos cardiovasculares nos doentes com psoríase não era a adequada. Por um lado, a taxa de subdiagnóstico e de subtratamento dos diversos factores de risco cardiometabólicos era extremamente elevada, condição particularmente importante por se tratar de uma população de maior risco. Por outro, verificámos que as actuais recomendações e objectivos terapêuticos para o tratamento dos factores de risco cardiovasculares e para a instituição de prevenção primária de eventos cardiovasculares poderão não ser os adequados para a população psoriática, uma vez que não têm em conta o aumento do risco atribuível à doença (*Framingham risk score* = 6.2%). Considerando este risco atribuível à psoríase grave, constatámos que uma proporção elevada de doentes com hipertensão arterial e hipercolesterolemia, considerados correctamente tratados segundo as orientações actuais, deixavam de o estar. Da mesma forma, nenhum doente com indicação para prevenção primária de eventos cardiovasculares se encontrava correctamente tratado.

A disfunção eréctil foi avaliada como possível marcador clínico de risco de doença cardiovascular em doentes com psoríase. Observou-se que a psoríase estava associada a uma maior prevalência e gravidade de disfunção eréctil, e que constituía um factor de risco independente de disfunção eréctil. Actualmente reconhece-se que a aterosclerose é uma importante causa de disfunção eréctil para além dos factores psicológicos. De facto, a disfunção eréctil precede habitualmente os eventos cardiovasculares, sendo considerada uma expressão de disfunção endotelial e um marcador de risco cardiovascular. Nos doentes estudados, a presença de lesões genitais ou de um *Dermatology Life Quality Index*

superior não se associou a disfunção eréctil, pelo que o componente psicológico inerente à psoríase não pareceu ser determinante nos resultados. Assim, a disfunção eréctil poderá ser um marcador de risco a considerar nos doentes com psoríase, podendo identificar precocemente os doentes em maior risco de doença cardiovascular.

Avaliámos neste projecto diferentes biomarcadores inflamatórios nos doentes com psoríase, em particular a sua influência no risco cardiometabólico. Descrevemos, pela primeira vez, que os níveis de C3 se encontravam elevados na psoríase, independentemente do perímetro abdominal, indicando que esta associação não se deve apenas ao excesso de adiposidade observada nestes doentes, mas provavelmente também é decorrente de mecanismos imunomediados inerentes à psoríase. Constatou-se ainda, que o C3 poderá ser um melhor marcador de risco cardiometabólico do que a proteína C-reactiva, pois, ao contrário desta, associou-se a vários marcadores de risco, como LDL oxidado, insulino-resistência e presença de síndrome metabólico. Estes resultados poderão ter implicações clínicas importantes, uma vez que o C3 poderá funcionar como um novo biomarcador na identificação de doentes psoriáticos com maior risco de desenvolver doença cardiovascular.

A gordura epicárdica, que não tinha ainda sido estudada na psoríase, foi avaliada nesta investigação. Demonstrámos, pela primeira vez, que a gordura epicárdica, estava aumentada nos doentes com psoríase, sendo este aumento independente da gordura visceral abdominal. Verificámos ainda, que na população com psoríase, a gordura epicárdica se associava a aterosclerose subclínica (avaliada por calcificação arterial coronária), independentemente da presença de outros factores de risco de aterosclerose. Estes resultados indicam que a gordura epicárdica é provavelmente mais um importante factor que contribui para o aumento do risco cardiovascular na psoríase e que poderá ser utilizada como um factor preditivo independente de aterosclerose coronária nestes doentes.

Por fim, a influência de factores genéticos no desenvolvimento de aterosclerose e/ou das comorbilidades cardiometabólicas nos doentes com psoríase também foi estudada. Os resultados obtidos sugerem que a associação entre a psoríase, comorbilidades cardiometabólicas e doença cardiovascular pode ser em parte geneticamente determinada e não exclusivamente adquirida.

Observámos que numa população pediátrica com psoríase, a prevalência de adiposidade excessiva assim como de alguns dos componentes do síndrome

metabólico, era significativamente superior à da população controlo. Adicionalmente observou-se um perfil lipídico alterado, mais aterogénico, nos doentes com psoríase, comparativamente com a população sem doença. A presença destas alterações numa idade pediátrica e especialmente numa fase inicial da doença sugerem uma influência genética no desenvolvimento de comorbilidades cardiometabólicas.

Na população adulta estudada demonstrámos, pela primeira vez, que a presença do alelo G do polimorfismo genético rs2069840 [-1753C/G] da IL-6 estava associada ao aumento do volume de gordura epicárdica em doentes com psoríase. Estes resultados podem constituir o primeiro passo para a identificação de biomarcadores genéticos que identifiquem os doentes em maior risco de desenvolver doença cardiovascular.

A investigação desenvolvida no âmbito desta tese contribuiu para uma melhor compreensão dos diversos factores que influenciam o desenvolvimento de doença cardiovascular e de comorbilidades cardiometabólicas nos doentes com psoríase. Permitiu ainda, identificar novos mecanismos nesta associação e encontrar marcadores clínicos e laboratoriais que podem ter um papel na identificação de doentes em maior risco. Salienta-se que estes resultados poderão ter implicações clínicas importantes, o principal objectivo da investigação clínica.

SUMMARY

Psoriasis is a chronic inflammatory disease, affecting 2 to 3% of the general populations, associated with decreased quality of life and high social and economic impacts.

Over the last few years the understanding of psoriasis as a disease evolved. It was primarily viewed as a simple skin disease, however, nowadays it is recognized as a systemic inflammatory disease associated with multiple comorbidities, particularly cardiometabolic. The increased risk of cardiovascular events observed in psoriasis patients versus the general population, with a consequent increase of mortality and a 5 to 6 years decrease of life expectancy was decisive to this classification. Increased cardiovascular risk factors and systemic inflammation, present especially in patients with severe psoriasis, have a crucial role in the early and accelerated atherosclerosis observed in such patients. The precise mechanisms responsible for such association are still not totally understood, although it is believed to be multifactorial, involving genetic, immunologic and environmental factors. Identifying genetic, laboratorial and clinical markers, enabling early recognition of patients at increased risk is essential and may carry significant practical implications as it would allow preventive and therapeutical measures that could ultimately decrease psoriasis associated cardiovascular mortality.

The main aim of this thesis was to evaluate potential genetic, laboratorial and clinical markers that could allow identifying psoriasis patient at higher risk of developing cardiometabolic comorbidities and cardiovascular disease. Particular emphasis was given to the study of the influence of genetic polymorphisms in the increased risk of cardiovascular disease in severe psoriasis patients, notably proinflammatory cytokines and adipokines known to have a role in the pathogenesis of psoriasis but also of other comorbidities and atherosclerosis. Additionally, other factors that could influence the increase of cardiovascular risk, as behaviour factors,

inflammation factors and recently identified risk markers for cardiovascular disease were also evaluated.

We observed that besides the psoriasis' intrinsic risk of cardiovascular disease, due to increased prevalence of cardiometabolic comorbidities and systemic inflammation, other factors, including behavioural and related to medical management of these patients, contribute to the increase of cardiovascular risk. We showed that physical activity and the proportion of patients who met the recommendations for healthy physical activity were significantly decreased in patients with psoriasis compared with the control group.

Furthermore, when studying the current approach of cardiovascular risk factors and primary prevention of cardiovascular events, we verified that it was not ideal, as a high rate of underdiagnosis and undertreatment of cardiovascular risk factors was observed. Moreover, it was noted that current recommendations and therapeutic goals for cardiovascular risk factors management and primary prevention of cardiovascular events are not ideal for the population understudy as the current indications do not take into account the increased risk attributable to this disease (Framingham risk score = 6.2%). Indeed, taking into account this increased risk attributable to severe psoriasis, we observed that a high proportion of patients with hypertension and hypercholesterolemia considered properly treated according to current guidelines, would no longer be considered as such, and no patients with indication for primary prevention of cardiovascular events was being properly treated.

Evaluating erectile dysfunction as a possible clinical marker for cardiovascular disease in patients with psoriasis, it was found that psoriasis was associated with an increased prevalence and severity of erectile dysfunction and that psoriasis was an independent risk factor for erectile dysfunction. Currently, in addition to psychological factors, it is recognized that atherosclerosis is a leading cause of erectile dysfunction. In fact, erectile dysfunction usually precedes cardiovascular events and is considered an expression of endothelial dysfunction and a marker of cardiovascular risk. In the psoriatic population the presence of genital lesions or a higher Dermatology Life Quality Index was not associated with higher erectile dysfunction, whereby the inherent psoriasis psychological component did not appear to be decisive in the results. Thus, erectile dysfunction may be a risk marker to be taken into account in patients with psoriasis, and may allow to early identify increased risk of cardiovascular disease.

Within this project, several inflammatory biomarkers were evaluated in patients with psoriasis, in particular their influence on cardiometabolic risk. We describe for the first time that levels of C3 are elevated in psoriasis, regardless of waist circumference, indicating that this association is not only due to excess adiposity observed in these patients, but also probably due to immune-mediated mechanisms. Additionally, it was found that C3 may be a better marker of cardiometabolic risk than C-reactive protein because, unlike the latter, it was associated with several cardiometabolic metabolic syndrome. These findings may have important clinical implications, since C3 may be used as a new biomarker in the identification of psoriatic patients with increased risk of cardiovascular disease.

Epicardial adipose tissue was also evaluated in psoriasis patients in this research. We have demonstrated for the first time that epicardial adipose tissue, a type of visceral adipose tissue surrounding the heart and coronary vessels, was increased in psoriasis patients, independently from abdominal visceral adiposity. Furthermore, in the psoriasis population, epicardial adipose tissue volume was associated with subclinical arteriosclerosis (evaluated by coronary artery calcification), independently from other arteriosclerosis risk factors. These results showed that epicardial adiposity is probably another important contributor to increased cardiovascular risk in psoriasis and may be used as an independent predictor of coronary arteriosclerosis in such patients.

Lastly, the influence of genetic factors in the development of arteriosclerosis and/or cardiometabolic comorbidities in patients with psoriasis was also evaluated. The results suggest that the association between psoriasis, cardiometabolic comorbidities and cardiovascular disease may be, in part, genetically determined rather than exclusively acquired. It was observed that in a pediatric population with psoriasis, the prevalence of excess adiposity as well as some metabolic syndrome components was significantly higher than in the control population. In addition, an altered lipid profile was observed in this population. The presence of these metabolic alterations at a pediatric age and notably at an early stage of the disease suggests a genetic influence in the development of cardiometabolic comorbidities.

In the adult population studied, we have demonstrated for the first time that the presence of the G allele of the IL-6 rs2069840 [-1753C/G] polymorphism was associated to an increased epicardial adipose tissue volume in psoriasis patients, a first step toward the identification of genetic biomarkers allowing to identify higher risk patients.

This project resulted in a better understanding of the various factors that influence the development of cardiovascular disease and cardiometabolic comorbidities in patients with psoriasis and in the identification of new mechanisms of this association. Moreover, new clinical, laboratory and genetic markers that may have a role in identifying patients at higher risk were found.

It is noted that these results may have important clinical implications, which should be the central objective in clinical research.

CAPÍTULO 1: INTRODUÇÃO

1. INTRODUÇÃO

A psoríase é uma doença inflamatória crónica que afecta 2-3% da população (1). Apesar de ter uma baixa mortalidade, tem um grande impacto na qualidade de vida dos doentes, estimando-se que seja igual ou superior ao observado noutras patologias como doenças oncológicas, artrite, doença cardíaca, diabetes e depressão (2). Adicionalmente este impacto na qualidade de vida parece ser cumulativo, uma vez que, muitas das decisões dos doentes são negativamente influenciadas pela doença ao longo da sua vida (3). A psoríase tem, também, um importante impacto na sociedade e nos sistemas de saúde. A produtividade laboral destes doentes é habitualmente menor, o absentismo maior, e os tratamentos actuais, embora cada vez mais eficazes, não são curativos e estão associados a custos cada vez mais elevados (4-6).

Nos últimos anos, a psoríase tem sido alvo de extensa investigação, com naturais implicações clínicas e terapêuticas. Devido à elevada prevalência e consequências na qualidade de vida dos doentes, a psoríase sempre foi uma importante patologia para os clínicos. No entanto, ao ser recentemente considerada uma doença sistémica, associada a múltiplas comorbilidades cardiometabólicas e a eventual aumento do risco cardiovascular, a sua abordagem sofreu alterações significativas. No campo da investigação, passou a constituir o principal modelo para estudo de mecanismos fisiopatológicos de inflamação crónica e a primeira escolha para avaliação de novas terapêuticas.

1.1. Manifestações clínicas e características histológicas da psoríase

A psoríase caracteriza-se pela presença de placas eritematosas, bem delimitadas, com descamação prateada, aderente e muitas vezes pruriginosas. Atinge habitualmente as superfícies extensoras (cotovelos e joelhos), couro cabeludo,

região lombo-sagrada e umbigo. Tem evolução crónica, com períodos de exacerbação, frequentemente modificada pelo início e/ou suspensão de tratamentos, sendo a remissão espontânea muito rara (7).

Estão descritos vários fenótipos de psoríase sendo a psoríase em placas a forma mais comum, afectando 80-90% dos doentes, caracterizando-se histologicamente por hiperplasia epidérmica, paraqueratose, hipogranulose, dilatação e proliferação vascular (angiogénese) e acumulação na derme de células inflamatórias, particularmente neutrófilos, células dendríticas e linfócitos T (8). Outras formas de psoríase menos comuns incluem: a psoríase inversa, que envolve as pregas cutâneas como as axilas ou as virilhas; a psoríase gutata, caracterizada por pequenas pápulas redondas dispersas, que ocorre mais frequentemente em crianças e geralmente após uma infecção respiratória por estreptococos β-hemolíticos do grupo A; a psoríase eritrodérmica, uma forma grave de psoríase caracterizada por eritrodermia; e a psoríase pustulosa que se manifesta por uma erupção pustulosa generalizada também esta grave e associada a febre e sintomas sistémicos. Por fim, também as unhas são frequentemente envolvidas (em cerca de 50% dos doentes), apresentado essencialmente picotado ungueal, hiperqueratose subungueal, mancha de óleo e onicólise (7).

1.2. Factores genéticos e ambientais

Actualmente, reconhece-se que a psoríase resulta da combinação de predisposição genética e de factores ambientais desencadeantes.

A importância do componente genético foi demonstrada em múltiplos estudos em famílias e em gémeos com psoríase. Esses estudos, mostraram que 71% das crianças com psoríase têm história familiar da doença(9) e que os familiares directos de doentes com psoríase têm um risco 4 vezes superior de desenvolver a doença, enquanto gémeos homozigóticos apresentam um risco 3 vezes superior de ambos terem psoríase comparativamente com gémeos dizigóticos (10).

Foram identificados, até ao momento, 36 regiões cromossómicas de susceptibilidade para psoríase (11). Contudo, apenas uma, localizada na região do Complexo de Histocompatibilidade Major (MHC) e denominada de PSOR1, tem sido consistentemente identificada em estudos genéticos (11). Esta região é responsável por 50% da susceptibilidade à psoríase. Incluído na região do PSORS1, o gene que parece ser mais relevante é o HLA-C, sendo o alelo HLA-Cw6*0602 o

principal alelo de risco (11). Este alelo é observado em 60% dos doentes com psoríase comparativamente com 15% na população geral e parece aumentar o risco de desenvolver psoríase em 10 a 20 vezes (12), especialmente em idade jovem (<40 anos) (13). Outros genes têm sido descritos (8) como estando associados a aumento de susceptibilidade de desenvolver psoríase, em particular genes envolvidos na regulação da resposta imune, embora a evidência científica seja ainda limitada.

Em indivíduos geneticamente predispostos, os factores ambientais são essenciais para o desenvolvimento da psoríase. Os mais comummente reconhecidos são as infecções bacterianas (especialmente nas formas gutata e pustulosa) mas também os traumatismos, a infecção por VIH, a hipocalcemia, o *stress* e a exposição a fármacos, como o lítio, β-bloqueadores, anti-maláricos, interferon ou a suspensão abrupta de corticoesteróides (14).

1.3. Fisiopatologia da psoríase

A psoríase foi considerada, até ao início dos anos 80, uma doença fundamentalmente dos queratinócitos na qual o infiltrado inflamatório cutâneo era um evento secundário. No entanto, desde a demonstração da eficácia da ciclosporina que a psoríase é considerada uma doença imunomediada. Apesar da evidência actual não permitir considerá-la uma doença auto-imune, a psoríase pertence provavelmente ao espectro das doenças relacionada com auto-imunidade, caracterizadas por inflamação crónica na ausência de um antigénio ou agente infeccioso conhecido (15).

A fisiopatogenia da psoríase é complexa, não estando ainda totalmente esclarecida; contudo, é reconhecido que tanto o sistema imune inato, como o adaptativo, são essenciais para o início e manutenção das lesões psoriáticas (8).

Na psoríase existe uma desregulação do sistema imune inato (16). As células apresentadoras de antigénios, particularmente as células dendríticas plasmocitóides e as células dendríticas mielóides, têm um papel fundamental no início da inflamação psoriática. As células dendríticas plasmocitóides são essenciais na produção de INF-α, um importante indutor das lesões psoriáticas, sendo activadas através da ligação dos seus receptores de superfície toll-like a complexos constituídos pelo peptídeo antimicrobiano catelecidina LL-37 e DNA, produzidos e libertados por queratinócitos, em resposta a factores ambientais

como trauma ou infecções (17). As células dendríticas mielóides são importantes na ligação entre a imunidade inata e a adaptativa através da activação e diferenciação dos linfócitos T (18). Adicionalmente têm um papel pró-infamatório, através de um subgrupo denominado de células dendríticas TIP, que produzem elevadas quantidades de TNF-α contribuindo para o ambiente inflamatório das lesões psoriáticas (19). Os queratinócitos, considerados até há pouco tempo secundários no processo inflamatório da psoríase, têm afinal um papel fundamental na fisiopatogenia da doença, não só nos eventos iniciais como na manutenção da inflamação psoriática (16). São uma importante fonte de peptídeos antimicrobianos, como a LL-37, β-defensinas e S100A7 que, para além do seu papel antimicrobiano, são também quimiotácticos e pró-inflamatórios (16, 20). Além da activação das células dendríticas plasmocitóides, participam também no recrutamento de diversas células infamatórias do sistema imune inato, como os neutrófilos, os mastócitos e os macrófagos, que vão contribuir fortemente para o ambiente inflamatório das lesões psoriáticas através da produção de múltiplas citocinas como o TNF-α, IL-6 ou IL-17 (16, 21, 22). Adicionalmente, os queratinócitos têm também um papel na resposta imunológica cutânea. Por um lado, respondem a citocinas inflamatórias produzidas pelas células T, como o INF-α, TNF-α, IL-17, IL-20 e IL-22, e por outro produzem várias citocinas pro-inflamatórias e quimiocinas (IL-8, CXCL10, CCL20), funcionando como um elo de ligação entre o sistema imune inato e adaptativo (16, 21).

A activação do sistema imune adaptativo decorre da interacção entre as células dendríticas mielóides e os linfócitos T (18). As células dendríticas mielóides activadas migram para os gânglios linfáticos e induzem a diferenciação de células T naive em célula T efectoras, especialmente Th1, Th17 e Th22, através da acção do TGF-β, IL-6, IL-12 e IL-23 (18). Posteriormente, os linfócitos T efectores migram para a pele através da interacção entre a α1β1 integrina dos linfócitos T e o colagénio IV da membrana basal onde produzem INF-γ (Th1), TNF-α (Th1 e Th17), IL-17 (Th17) e IL-22 (Th22) que são essenciais para a expressão da doença (14). Estes mediadores actuam nos queratinócitos conduzindo à sua activação, proliferação e produção dos múltiplos mediadores inflamatórios descritos anteriormente, criando um ciclo vicioso inflamatório.

A angiogénese observada na psoríase decorre especialmente da produção de VEGF pelos queratinócitos e pelos mastócitos (23).

Por fim, também os mecanismos imunológicos de regulação se encontram alterados na psoríase. Apesar de alguns estudos não terem mostrado que o número de células T reguladoras esteja diminuído nas lesões psoriáticas (24),

provavelmente existe um defeito na sua actividade, uma vez que a IL-10, uma importante citocina reguladora, está diminuída na psoríase, o que poderá ser em parte devido ao excesso de IL-6 (25).

1.4. Comorbilidades cardiometabólicas e doença cardiovascular na psoríase

Nos últimos anos, a psoríase deixou de ser vista como uma doença exclusivamente cutânea. Actualmente, é considerada uma doença inflamatória sistémica associada a múltiplas comorbilidades, em particular, cardiometabólicas (26). Especialmente nos casos mais graves, o estado inflamatório não parece confinar-se apenas à pele. De facto, as diferentes citocinas que participam na fisiopatogenia da psoríase encontram-se elevadas sistemicamente e correlacionam-se com a gravidade da doença, assim como muitos outros biomarcadores de inflamação sistémica (26, 27). A principal consequência deste estado inflamatório crónico sistémico é o aumento do risco de eventos cardiovasculares (Acidente Vascular Cerebral [AVC] e Enfarte Agudo do Miocárdio [EAM]) e da mortalidade cardiovascular com uma diminuição da esperança média de vida em cerca de 5-6 anos (28-30). A associação entre psoríase e doença cardiovascular foi descrita pela primeira vez em 1978 por McDonalds e Calabresi, quando mostraram que o risco de doença vascular arterial e venosa (EAM, AVC e embolia pulmonar) nos doentes com psoríase era 2.2 vezes superior comparativamente com uma população controlo com outras doenças dermatológicas (31). Desde então, vários estudos epidemiológicos com um elevado número de doentes confirmaram estes dados, mostrando um aumento do risco de eventos e de mortalidade cardiovascular (32-34), mesmo após ajuste aos diferentes factores de risco de doença cardiovascular, sugerindo que a psoríase poderá ser um factor de risco independente de doença cardiovascular.

Uma meta-análise recente, que avaliou um total de 201239 doentes com psoríase ligeira e 17415 doentes com psoríase grave, mostrou que a psoríase (ligeira e grave) se associava a risco significativamente aumentado de EAM, de AVC e de mortalidade cardiovascular, sendo este risco superior nos casos de doença grave.

Assim, o risco relativo estimado de EAM na psoríase grave era de 1.70 (95% CI: 1.32-2.48), de AVC de 1.56 (95% CI: 1.32-1.84) e de mortalidade cardiovascular 1.39 (95% CI: 1.11-1.74)(35). Recentemente, num estudo efectuado com 3603 doentes com psoríase grave foi estimado que a psoríase grave poderá conferir um aumento em 6.2% no *Framingham Risk Score* (FRS), isto é, no risco de eventos cardiovasculares *major* a 10 anos (36).

A razão para esta associação ainda é desconhecida, mas será certamente multifactorial, envolvendo factores genéticos, imunológicos e ambientais. No entanto, o aumento da prevalência e incidência de comorbilidades cardiometabólicas (obesidade, dislipidemia, HTA, insulino-resistência/DM) nos doentes com psoríase e a inflamação sistémica, presente essencialmente nos casos mais graves, parecem ser essenciais nesta associação (23, 37).

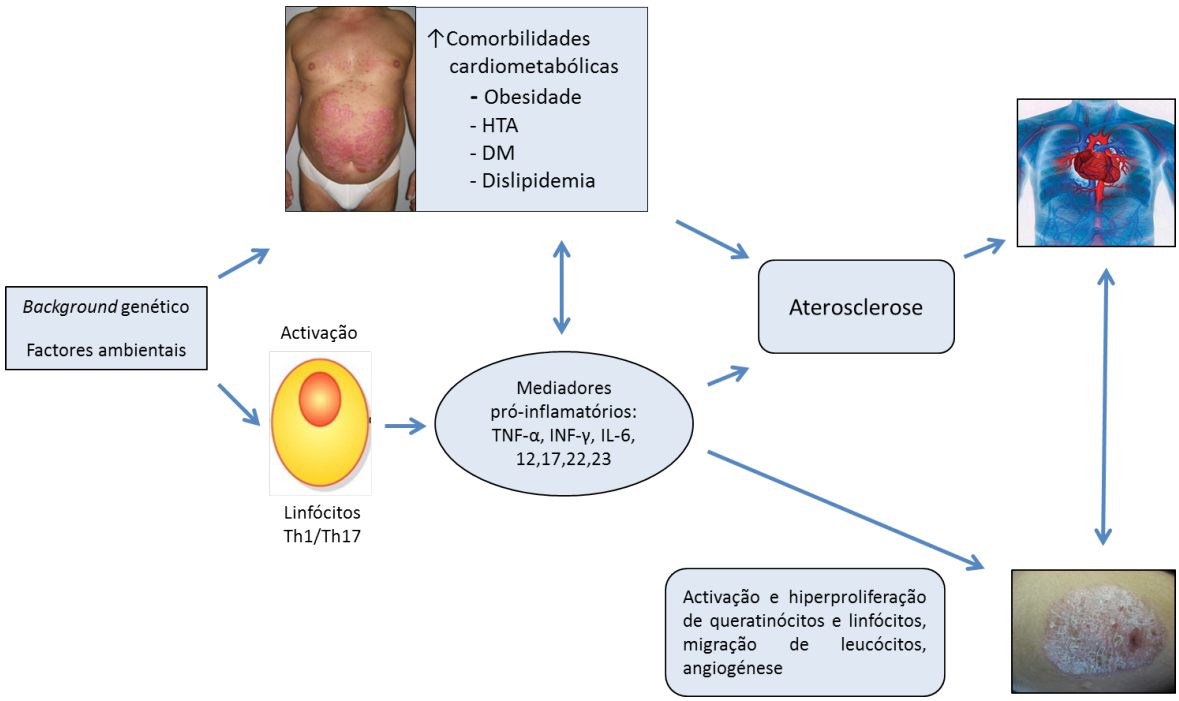

Figura 1 | Adaptado de: Torres T, *et al*. Psoriasis and cardiovascular disease. Acta Med Port 2013;26:601-7.

O impacto destas comorbilidades cardiometabólicas e aterosclerose acelerada nos doentes psoriáticos é extremamente elevado, não só reduzindo a esperança média de vida como também aumentando o risco de efeitos secundários de várias terapêuticas utilizadas na psoríase (38, 39). Adicionalmente, esse impacto é ainda relevante para a sociedade e sistemas de saúde. Recentemente foi demonstrado que os doentes psoriáticos com comorbilidades, particularmente cardiovasculares, consomem mais recursos de saúde, aumentando os custos associados à doença comparativamente aos doentes sem comorbilidades (40).

1.4.1. Obesidade

Múltiplos estudos epidemiológicos têm mostrado que o risco de obesidade é significativamente superior nos doentes com psoríase relativamente à população geral. Uma revisão sistemática e meta-análise dos estudos observacionais,

envolvendo um total de 2.1 milhões de participantes (201831 com psoríase), confirmou esta associação (OR 1.66; 95% CI: 1.46-1.89). Quando avaliada a relação com a gravidade da psoríase, o risco de obesidade foi superior nos doentes com psoríase grave comparativamente com casos de psoríase ligeira (OR 2.23; 95% CI: 1.63-3.05 vs OR 1.46; 95% CI: 1.17-1.82). Foi também observado que os doentes com psoríase tinham um risco superior de desenvolver obesidade comparativamente com os controlos (HR 1.18; 95% CI:1.14-1.23) (41).

A obesidade parece ter um papel central na ligação entre a psoríase, as diversas comorbilidades cardiometabólicas e a doença cardiovascular, que se deve sobretudo à actividade imunológica e endocrinológica da gordura visceral (42, 43). De facto, a gordura visceral, em oposição à gordura subcutânea, é actualmente considerada um tecido metabolicamente activo, que produz inúmeras citocinas e adipocinas com um papel estabelecido na aterosclerose e na insulino-resistência (44, 45), tendo sido demonstrado que se encontra aumentada na psoríase (46). Desta forma, sabe-se actualmente que a obesidade se associa a um estado persistente de inflamação caracterizada por níveis elevados de TNF-α, IL-6, IL-8, MCP-1, leptina e resistina e por níveis diminuídos de adiponectina, uma adipocina com propriedades anti-inflamatórias (47).

A razão desta associação é multifactorial, envolvendo factores genéticos, imunológicos e ambientais, sendo provável que esta relação seja bidireccional. Por um lado, a inflamação presente na psoríase, especialmente através do TNF-α e IL-6, parece promover o recrutamento e activação de macrófagos na gordura visceral com um aumento da produção de TNF-α, não só induzindo um estado pró-inflamatório, como também estimulando os adipócitos a produzir diversos mediadores inflamatórios, como MCP-1 (que recrutam ainda mais macrófagos), IL-6 e diversas adipocinas inflamatórias (leptina, resistina, visfatina), que aumentam e perpetuam a inflamação associada ao excesso de adiposidade (48). Por outro lado, o estado inflamatório associado à obesidade aumenta a gravidade da psoríase. Muitas destas adipocinas encontram-se também elevadas na psoríase e poderão ser um importante elo de ligação entre as duas patologias (42).

A melhoria da psoríase, assim como da resposta aos tratamentos, observada com a perda de peso é igualmente a favor de uma relação intrínseca entre as duas patologias, e provavelmente devido à diminuição da inflamação associada à perda de gordura visceral (49).

1.4.2. Hipertensão arterial

A associação entre psoríase e hipertensão arterial tem sido sugerida em múltiplos estudos epidemiológicos. Numa revisão sistemática e meta-análise de estudos observacionais, envolvendo 309469 doentes com psoríase, o OR estimado para HTA nos doentes com psoríase foi de 1.58 (95% CI: 1.42-1.76) comparativamente com os controlos, sendo este risco superior nos doentes com psoríase grave relativamente a formas mais ligeiras (OR 1.49; 95% CI: 1.20-1.86 vs OR 1.30; 95% CI: 1.15-1.47). Dois estudos avaliando a incidência de HTA nestes doentes mostrou que a psoríase se associava a um HR de 1.09 (95% CI: 1.05-1.14) (50).

Embora os mecanismos exactos responsáveis por esta associação sejam ainda desconhecidos, é possível que o aumento da prevalência da obesidade assim como a desregulação do sistema de angiotensina-renina, a produção de níveis elevados de endotelina-1 pelos queratinócitos e o stress oxidativo (promovendo alterações da vasodilatação dependente do endotélio) observado nos doentes com psoríase (23, 51-53) expliquem em parte esta associação.

1.4.3. Dislipidemia

Existe, igualmente, evidência científica de que a prevalência e incidência de dislipidemia (hipercolesterolemia e hipertrigliceridemia) está aumentada nos doentes com psoríase, suportando a possibilidade destas doenças partilharem vias inflamatórias e genéticas comuns.

Uma revisão sistemática da literatura recente, envolvendo 25 estudos observacionais com um total de 2.4 milhões de participantes, dos quais 265512 tinham psoríase, mostrou que a psoríase se associava a dislipidemia em 80% dos estudos, com um OR para dislipidemia entre 1.04 e 5.55. Avaliando o risco de hipertrigliceridemia (definida nestes estudos como valor plasmático de triglicerídeos>150mg/dL) os doentes com psoríase apresentavam um OR entre 1.20 a 4.98. Finalmente, três estudos mostraram que os doentes com psoríase tinham um risco aumentado entre 1.36 a 1.77 de terem HDL<40mg/dL. Quando avaliada a relação com gravidade de psoríase, o risco de dislipidemia era superior nos casos mais graves (54).

Uma possível explicação envolve o papel de certas citocinas implicadas na psoríase, nomeadamente IL-1, IL-6 e TNF-α que parecem também participar na desregulação e elevação do perfil lipídico. Por um lado, parecem estar envolvidas na inibição da actividade da lípase de lipoproteínas, diminuindo a metabolização

dos triglicerídeos e aumentando consequentemente o seu nível no plasma. Por outro, estas citocinas também aumentam a lipólise e estimulam a síntese hepática de ácidos gordos, resultando na elevação sérica de lípidos (55-57). Estes mecanismos imunológicos também explicariam a razão pela qual os casos mais graves de psoríase se associam a um maior risco de dislipidemia comparativamente com situações mais ligeiras.

1.4.4. Insulino-resistência e diabetes

Vários estudos têm demonstrado uma associação entre psoríase e insulino-resistência/diabetes, de forma independente de outros factores de risco, como a obesidade e a dislipidemia. Uma meta-analise que incluiu 27 estudos observacionais, demonstrou que a psoríase se associava a uma prevalência e incidência aumentada de diabetes, OR 1.59 (95% CI: 1.38-1.83) e RR 1.27 (95% CI: 1.16-1.40) respectivamente, em especial nos doentes com psoríase grave (psoríase ligeira: OR 1.53; 95% CI: 1.16-2.04 e psoríase grave: OR 1.97; 95% CI: 1.48-2.62) (58).

Esta associação poderá ser explicada por um fundo genético comum, mas também pelo efeito da inflamação sistémica presente na psoríase (23, 37, 59). O TNF-α e a IL-6 têm um papel importante na regulação da sensibilidade à insulina. O TNF-α pode induzir insulino-resistência através da inibição da actividade da cinase de tirosina do receptor de insulina e também pela inibição da secreção de adiponectina pelos adipócitos(60), enquanto a IL-6 pode promover insulino-resistência pela sua intervenção no receptor de insulina (61).

1.4.5. Aterosclerose

Existe evidência crescente que a inflamação sistémica presente na psoríase poderá ser um factor de risco independente de aterosclerose, por promover disfunção endotelial, uma das primeiras fases da aterosclerose, tal como ocorre noutras doenças infamatórias crónicas como a artrite reumatóide ou o lúpus eritematoso sistémico. De facto, são vários os estudos que demonstraram que a psoríase é um factor de risco independente de aterosclerose, utilizando diversos marcadores, como a calcificação arterial coronária, o espessamento da camada intima-média da artéria carotídea, a rigidez arterial, entre outros (62-64).

A psoríase e a aterosclerose parecem partilhar diversas vias inflamatórias e mecanismos fisiopatogénicos, como processos imunológicos (activação e migração de células T, expressão de moléculas de adesão, angiogénese), células (linfócitos

Th1 e Th17, células dendríticas, macrófagos, neutrófilos) e citocinas envolvidas (IL-2, IL-8, IL-17, IL-23, TNF-α, VEGF) (23, 37, 65).

A inflamação da psoríase caracteriza-se por elevados níveis de TNF-α, INF-α, INF-γ, IL-1, IL-6 e IL-17, que são produzidos pelos queratinócitos e diferentes células inflamatórias que infiltram a pele, e que, especialmente nos casos mais graves, também se encontrem elevados a nível sistémico (26, 27). Estas citocinas promovem múltiplos efeitos pró-aterogénicos como resistência à insulina, dislipidemia, *stress* oxidativo e disfunção endotelial (66). Em particular o TNF-α promove disfunção endotelial através da diminuição da expressão da síntase de óxido nítrico e da cicloxigenase-1 (67). Além destes efeitos, estas citocinas têm ainda a capacidade de promover múltiplas funções pró-aterogénicas hepáticas e do tecido adiposo, incluído a produção de proteína C-reactiva, IL-6, fibrinogénio e múltiplas adipocinas, como a leptina e resistina (68).

O termo "marcha psoriática" tem sido utilizado para descrever um processo progressivo que explica a ligação entre psoríase e doença cardiovascular. Assim, a inflamação crónica existente na psoríase seria responsável não só pelas manifestações cutâneas mas também pelo desenvolvimento de diferentes comorbilidades e em particular da doença cardiovascular (69). Este modelo postula que a inflamação sistémica associada à psoríase induz insulino-resistência, causando disfunção endotelial, aterosclerose e eventualmente eventos cardiovasculares.

Finalmente, a demonstração da redução do risco de eventos cardiovasculares com a utilização de agentes inibidores do TNF-α é outra importante evidência que confirma o papel da inflamação psoriática no desenvolvimento de aterosclerose e doença cardiovascular (70).

1.5. Influência genética na associação entre psoríase, comorbilidades cardiometabólicas e doença cardiovascular

É provável que factores genéticos contribuam para a associação entre psoríase e as comorbilidades cardiometabólicas e doença cardiovascular.

Reconhece-se, actualmente, que a susceptibilidade genética tem um papel no desenvolvimento da psoríase (71, 72), assim como, das diferentes comorbilidades cardiometabólicas e mesmo da doença cardiovascular (73-75). No entanto a evidência da influência e importância de factores genéticos no desenvolvimento de comorbilidades e doença cardiovascular nos doentes com psoríase é ainda

limitada. Um estudo de associação genética de 2009 identificou pelo menos 21 *loci* genéticos distintos que contribuiriam para o desenvolvimento de doença cardiovascular (76). No entanto, nenhum dos genes identificados correspondia ou fazia parte de *loci* de susceptibilidade da psoríase. Contudo, outros estudos identificaram marcadores genéticos comuns à psoríase e algumas destas doenças metabólicas, como o CDKALI na diabetes tipo 2, APOE4 na dislipidemia e TNFAIP3 na doença coronária (59, 77-80).

Mais recentemente, Lu, *et al*, seleccionou 363 *single-nucleotide polymorphisms* (SNPs) que mostraram uma associação significativa com doença arterial coronária, hipertensão, obesidade, hiperlipidemia e diabetes tipo 2 em estudos de associação genética anteriores, e avaliou a sua associação com psoríase em 4 coortes envolvendo um total de 4476 doentes com psoríase e 7463 controlos (81). Neste trabalho, os autores mostraram que os doentes com psoríase apresentavam algumas variantes genéticas que predispunham a um aumento do risco de dislipidemia, hipertensão e doença arterial coronária, como FUT2, UBE2L3 ou SH2B3 (81).

Apesar destes estudos de associação serem importantes para identificar genes e vias patogénicas para investigação futura é essencial analisar a sua associação com aterosclerose e comorbilidades cardiometabólicas em doentes com psoríase. Entre os genes que também poderão ser factores de risco comuns à psoríase e doenças metabólicas estão os genes de um alargado conjunto de citocinas (TNF-α, IL-6, VEGF, endotelina-1), adipocinas (leptina, adiponectina) e seus receptores, que têm um papel reconhecido na fisiopatogenia das diferentes patologias.

A IL-6 é uma citocina envolvida em vários processos fisiológicos e patológicos, particularmente na reposta inflamatória, sendo produzida por diferentes células incluindo os linfócitos, monócitos, fibroblastos, células endoteliais e adipócitos (82, 83). A IL-6 tem sido implicada na fisiopatogenia de diversas doenças inflamatórias crónicas, incluindo a psoríase, participando na diferenciação das células Th17 e na inflamação cutânea induzida pela IL-23, que não ocorre sem a participação da IL-6 (27, 84-86), mas também da obesidade (87, 88), aterosclerose (89, 90) e doença cardiovascular (91).

O TNF-α é uma citocina pró-inflamatória produzida por inúmeras células incluindo monócitos e macrófagos activados, linfócitos, mastócitos e células NK, que tem sido implicado na patogénese de inúmeras doenças imunomediadas, incluído a psoríase (8). O TNF-α tem sido igualmente envolvido na patogénese das

comorbilidades cardiometabólicas associadas à psoríase (HTA, insulino-resistência, dislipidemia e obesidade) (48) e também na inflamação que acompanha a aterosclerose (92). Vários estudos demonstraram a associação entre as concentrações séricas de TNF-α e o risco de doença cardiovascular (93).

A leptina é sintetizada predominantemente pelos adipócitos, estando implicada na regulação do peso corporal, gasto energético e apetite (42, 94). Participa igualmente na modulação da imunidade inata e adaptativa, actuando em processos de inflamação aguda e crónica (95). A leptina actua na modulação da actividade das células T, promovendo as respostas Th1, induzindo a produção de IL-2 e INF-γ, e inibindo as células Treg. Na imunidade inata, promove a actividade dos macrófagos, resultando na produção de IL-1β, IL-6, IL-12 e TNF-α. Desta forma, a leptina poderá estar envolvida na patogénese da psoríase, pela síntese de citocinas da via Th1 e diminuição da actividade de linfócitos Treg (42, 96), e igualmente na aterosclerose (97) e obesidade (43). De facto, níveis elevados de leptina têm sido associados a psoríase (42) e doença cardiovascular (98).

A adiponectina é produzida essencialmente pelos adipócitos, exercendo efeitos insulino-sensibilizantes, anti-inflamatórios e ateroprotectores, através da redução da expressão de moléculas de adesão vascular (VCAM-1), citocinas pró-inflamatórias (TNF-α, IL-6 e IL-8), espécies reactivas de oxigénio nas células endoteliais (42, 99) e pela indução de citocinas anti-inflamatórias como IL-10 e o antagonista do receptor da IL-1. A sua secreção encontra-se diminuída na obesidade (100), diabetes tipo 2 (101) e doença arterial coronária (102) e, nos últimos anos, vários estudos têm demonstrado que também na psoríase, os níveis de adiponectina estão diminuídos (42).

A expressão dos genes responsáveis por estas moléculas é fortemente influenciada por variações genéticas (103-105) pelo que, a presença de certos polimorfismos genéticos poderá ser responsável pelo desenvolvimento de psoríase e também das diferentes comorbilidades. Contudo, estudos avaliando a influência de variantes genéticas destas citocinas e adipocinas no risco de comorbilidades cardiometabólicas, aterosclerose, ou doença cardiovascular em doentes com psoríase, usando marcadores específicos, estão ainda por desenvolver.

1.6. Objectivos da tese

A associação entre psoríase, comorbilidades cardiometabólicas e doença cardiovascular está bem definida existindo extensa literatura comprovando esta

associação. No entanto, os mecanismos fisiopatológicos não estão ainda totalmente esclarecidos, em particular a influência de factores genéticos.

A identificação de doentes com psoríase em maior risco de desenvolver comorbilidades ou doença cardiovascular é de extrema importância, uma vez que permitiria uma abordagem e tratamento mais precoce e mais agressiva dos diferentes factores de risco cardiovasculares, assim como a adopção de estilos de vida saudáveis, como a cessação tabágica e a prática de exercício físico regular.

O principal objectivo desta tese foi avaliar possíveis marcadores clínicos e laboratoriais (genéticos e analíticos) que permitissem a identificação de doentes em maior risco de desenvolver comorbilidades cardiometabólicas e doença cardiovascular. Foi dado especial destaque à influência de polimorfismos genéticos de citocinas pró-inflamatórias e adipocinas, conhecidas por terem um papel na fisiopatologia da psoríase assim como das diversas comorbilidades e aterosclerose, no aumento do risco de doença cardiovascular em doentes com psoríase grave. Avaliaram-se ainda outros factores que podem ter influência no aumento do risco de doença cardiovascular nestes doentes, como factores comportamentais, inflamatórios e marcadores de risco de doença cardiovascular recentemente identificados.

Objectivos específicos

- Avaliar a presença de factores de risco de doença cardiovascular relacionados com o estilo de vida (exercício físico) nos doentes com psoríase grave;
- Avaliar o impacto da psoríase no diagnóstico e tratamento dos factores de risco cardiovasculares;
- Avaliar a presença e gravidade de disfunção eréctil em doentes com psoríase grave, como marcador precoce de doença cardiovascular;
- Avaliar a influência do factor de complemento C3 no perfil cardiometabólico em doentes com psoríase grave;
- Avaliar a gordura epicárdica e a calcificação arterial coronária em doentes com psoríase grave;
- Avaliar a presença de factores de risco de doença cardiovascular em doentes com psoríase em idade pediátrica;
- Identificar marcadores genéticos associados a maior risco de doença cardiovascular nos doentes com psoríase grave (polimorfismos genéticos da IL-6, TNF-α, leptina, receptor da leptina, adiponectina).

Esta tese foi estruturada de forma a apresentar todos os artigos publicados no decorrer deste projecto de investigação (artigos de revisão e artigos originais), seguindo-se a discussão e conclusão.
Os artigos estão incluídos no próximo capítulo.

Artigos de revisão

- Psoríase, comorbilidades cardiometabólicas e doença cardiovascular:
  - *Psoriasis and cardiovascular disease*. Acta Med Port. 2013;26:601-7.
- Psoríase e obesidade:
  - *Obesity: a key component of psoriasis*. (submetido)
- Psoríase e síndrome metabólico:
  - *Psoriasis and metabolic syndrome*. Acta Dermatovenerol Croat. 2014.
- Importância da abordagem multidisciplinar dos doentes com psoríase:
  - *Psoriasis: The visible killer*. Rev Port Cardiol. 2014;33:95-9.
- Importância da avaliação da influência genética na associação psoríase/doença cardiovascular:
  - *Genetic markers for cardiovascular disease in psoriasis: the missing piece.* Mol Diagn Ther. 2014;18:93-5.

Artigos originais

- Actividade física em doentes com psoríase:
  - *Levels of Physical Activity in Patients with Severe Psoriasis: A Cross-Sectional Questionnaire Study.* Am J Clin Dermatol. 2014;15:129-35.
- Impacto da psoríase no diagnóstico e tratamento dos factores de risco cardiovasculares e na prevenção primária de eventos cardiovasculares:
  - *Framingham Risk Score underestimates cardiovascular disease risk insevere psoriatic patients: Implications in cardiovascular risk factors management and primary prevention of cardiovascular disease*. J Dermatol. 2013;40:923-6.
- Disfunção eréctil como marcador de risco cardiovascular em doentes com psoríase:
  - *Erectile dysfunction in psoriasis patients*. Eur J Dermatol. 2014
- Complemento C3 como marcador de risco cardiometabólico em doentes com psoríase:
  - *Complement C3 as a marker of cardiometabolic risk in psoriasis*. Arch Dermatol Res. 2014 May 22.

- Gordura epicárdica e calcificação arterial coronária em doentes com psoríase:
  - *Epicardial adipose tissue and coronary artery calcification in psoriasis patients*. J Eur Acad Dermatol Venereol. 2014 Apr 21.
- Comorbilidades cardiovasculares na psoríase em idade pediátrica:
  - *Cardiovascular comorbidities in childhood psoriasis.* Eur J Dermatol. 2014;24:229-35.
- Influência de polimorfismos genéticos da IL-6 na gordura epicárdica e calcificação arterial coronária em doentes com psoríase:
  - *Influence of IL-6 gene polymorphisms in epicardial adipose tissue and coronary artery calcification in psoriasis patients*. Br J Dermatol. 2014.
- Influência de polimorfismos genéticos do TNF-α na calcificação arterial coronária em doentes com psoríase:
  - *Influence of TNF-α gene polymorphisms in coronary artery calcification in psoriasis patients*. J Eur Acad Dermatol Venereol. 2014
- Influência de polimorfismos genéticos da leptina, receptor da leptina e adiponectina na gordura epicárdica, gordura visceral abdominal e calcificação arterial coronária em doentes com psoríase:
  - *Lack of association between leptin, leptin receptor and adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat and atherosclerotic burden in psoriasis patients* (submetido).

CAPÍTULO 2: ARTIGOS PUBLICADOS

Psoríase, Comorbilidades Cardiometabólicas e Doença Cardiovascular

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Torres T, Sales R, Vasconcelos C, Selores M.
Psoriasis and cardiovascular disease. *Acta Med Port*. 2013 Sep-Oct;26(5):601-7.

Psoríase e Doença Cardiovascular

ARTIGO DE REVISÃO

Psoriasis and Cardiovascular Disease

Tiago TORRES[1,2], Rita SALES[2], Carlos VASCONCELOS[2,3], Manuela SELORES[1,3]
Acta Med Port 2013 Sep-Oct;26(5):601-607

RESUMO

A psoríase é uma doença inflamatória sistémica crónica, frequente, associada a várias comorbilidades, destacando-se a obesidade, a hipertensão arterial, a diabetes, a dislipidemia e síndrome metabólico. Adicionalmente associa-se também a aumento do risco de doença cardiovascular – enfarte agudo do miocárdio e acidente vascular cerebral. A inflamação sistémica crónica presente na psoríase tem sido sugerida como um factor de risco independente para estas comorbilidades e para o aparecimento de aterosclerose precoce. Esta revisão das várias comorbilidades cardio-metabólicas e do risco de doença cardiovascular associado à psoríase tem como objectivo promover o conhecimento e alertar os clínicos para a necessidade de rastreio, monitorização e tratamento dos factores de risco de doença cardiovascular nestes doentes.
Palavras-chave: Psoríase; Doenças Cardiovasculares; Aterosclerose, Inflamação; Comorbilidade.

ABSTRACT

Psoriasis is a common, chronic and systemic inflammatory disease associated with several comorbidities, such as obesity, hypertension, diabetes, dyslipidaemia and metabolic syndrome, but also with an increased risk of cardiovascular disease, like myocardial infarction or stroke. The chronic inflammatory nature of psoriasis has been suggested to be a contributing and potentially independent risk factor for the development of cardiovascular comorbidities and precocious atherosclerosis. Aiming at alerting clinicians to the need of screening and monitoring cardiovascular diseases and its risk factors in psoriatic patients, this review will focus on the range of cardiometabolic comorbidities and increased risk of cardiovascular disease associated with psoriasis.
Keywords: Psoriasis; Cardiovascular Diseases; Atherosclerosis; Inflammation; Comorbidity.

INTRODUÇÃO

A psoríase é uma doença inflamatória crónica, imuno-mediada que afecta aproximadamente 2 a 3% da população mundial, associada a marcada redução da qualidade de vida dos doentes.[1]

Durante décadas a psoríase foi considerada uma doença primariamente do queratinócito. No entanto, desde a demonstração do efeito terapêutico da ciclosporina em 1979, que passou a ser reconhecida como uma doença imuno-mediada em que tanto a imunidade inata como a adquirida têm um papel preponderante na iniciação e manutenção das lesões cutâneas.[2] Nos últimos anos tem-se ainda demonstrado que a inflamação na psoríase não é exclusivamente cutânea, mas que existe uma inflamação sistémica, especialmente nos doentes mais graves, com elevação sérica de várias citoquinas inflamatórias, como o TNF-α, IL-6, IL-12, IL-17, IL-20, IL-22 e IL-23.[3]

Vários trabalhos demonstraram maior incidência de obesidade, diabetes mellitus (DM), hipertensão arterial (HTA), síndrome metabólico e doença cardiovascular, como enfarte agudo do miocárdio (EAM) e acidente vascular cerebral (AVC) nos doentes com psoríase.[4-7] Acresce a esta maior incidência de factores de risco de doença cardiovascular, a inflamação sistémica que parece ter um papel importante no desenvolvimento de aterosclerose e doença cardiovascular[8] em particular nas formas mais graves e prolongadas da doença.

Assim, o componente cutâneo da psoríase pode ser, em muitos doentes, apenas a 'ponta do *iceberg*'. (Fig. 1)

Nesta revisão da literatura, os autores vão abordar as forma clínicas de psoríase e a sua associação com factores de risco cardiovasculares, inflamação sistémica e a hipótese de a psoríase constituir *per se* um factor de risco de doença cardiovascular.

Formas clínicas de psoríase

A psoríase caracteriza-se pela presença de placas eritematosas, descamativas, muitas vezes pruriginosas ou dolorosas. Tem um curso crónico com fases de agravamento e de acalmia, raramente com remissões espontâneas.[1]

Existem várias formas: a psoríase em placas é a mais comum e afecta cerca de 80 a 90% dos doentes. Caracteriza-se por placas eritematosas, bem definidas, de vários tamanhos, habitualmente recobertas por descamação prateada, localizando-se geralmente no couro cabeludo, tronco, cotovelos e joelhos, distribuindo-se frequentemente de forma simétrica. Aproximadamente 80% dos doentes tem uma forma ligeira, enquanto 20% tem formas moderadas a graves, com envolvimento de mais de 10% da superfície corporal, necessitando habitualmente de terapêutica sistémica ou fototerapia.[1]

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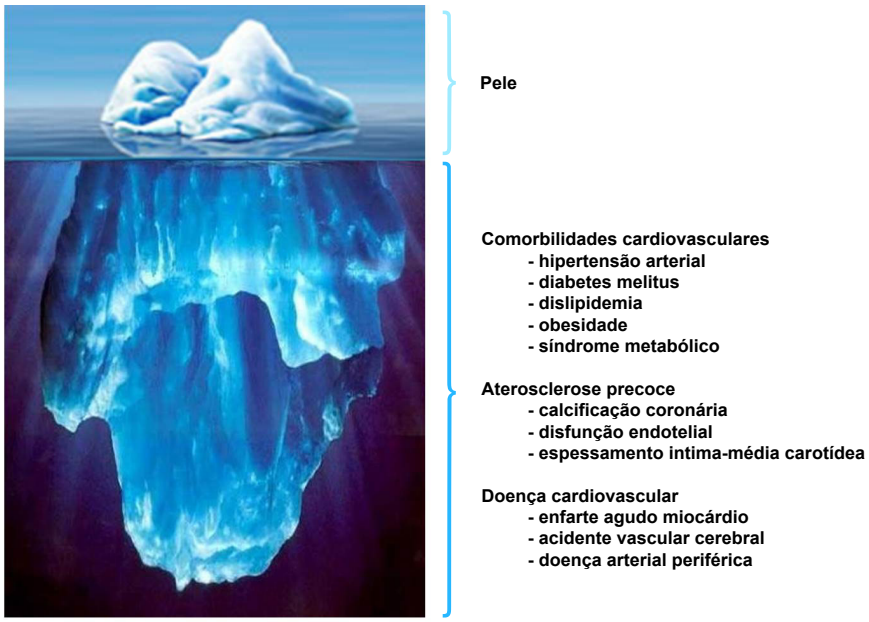

Figura 1 – Comorbilidades associada à psoríase

Na psoríase inversa as lesões localizam-se às pregas cutâneas axilares, inguinais, perineais, interglúteas e infra-mamárias e, devido a maior humidade destes locais, as lesões tendem a ser mais eritematosas e menos descamativas.

A forma gutata caracteriza-se por pequenas pápulas com descamação fina e ocorrem mais frequentemente em indivíduos jovens, sendo muitas vezes desencadeadas por infecções respiratórias superiores por estreptococos β-hemolíticos do grupo A.

Formas mais graves incluem a psoríase pustulosa e psoríase eritrodérmica, em alguns casos necessitando de internamento hospitalar. A psoríase pustulosa caracteriza-se por múltiplas pústulas que podem ser localizadas ou generalizadas. A forma generalizada (variante de *von Zumbush*) é uma forma aguda, grave, associada a sintomas sistémicos e febre. A psoríase eritrodérmica, manifesta-se por eritema envolvendo mais de 90% da superfície corporal, habitualmente com sintomas sistémicos.

Em todas as formas pode existir envolvimento ungueal. Este ocorre em mais de 50% dos doentes, incluindo picotado ungueal, onicólise, hiperqueratose subungueal e mancha de óleo.[1]

Doença Cardiovascular

A associação entre doença cardiovascular e psoríase foi descrita há quase 50 anos, mas foi na última década que se observou um aumento do interesse e da investigação nesta área. Assim, têm sido publicados vários estudos de coorte e populacionais que têm demonstrado esta associação.[4-6,9-11] E se no início, a maioria dos estudos avaliavam apenas a prevalência de factores de risco cardiovasculares, os trabalhos mais recentes estudaram especialmente a incidência de eventos cardiovasculares nos doentes com psoríase.

Gelfand et al[6] reportou, num estudo prospectivo envolvendo 130 976 doentes com psoríase e 556 995 controlos, que a psoríase se associava a um risco significativamente aumentado de EAM, mesmo efectuando análise multivariada com os vários factores de risco cardiovasculares como diabetes, história familiar de EAM, hipertensão, tabaco e índice de massa corporal. O risco relativo de EAM era maior para doentes jovens com psoríase (< 30 anos) com um *hazard ratio* (HR) de 1,29 e 3,10 para psoríase ligeira e grave respectivamente, enquanto nos mais velhos (>60 anos) o HR era de 1,08 e 1,36.

Noutro estudo com 3 236 doentes com psoriáticos e 2 500 controlos, e após ajuste aos vários factores de risco tradicionais de doença cardiovascular, observou-se, não só uma prevalência superior de doença cardíaca isquémica, mas também de doença cerebrovascular e de doença vascular periférica.[12] Ahlehoff et al[13] reportou, num estudo efectuado na Dinamarca envolvendo 36765 doentes com psoríase ligeira e 2 793 doentes com psoríase grave, um risco relativo de AVC em doentes com menos de 50 anos de 1,97 (95% CI, 1,66-2,34) e 2,80 (1,81-4,34) respectivamente, diminuindo ligeiramente nos doentes com mais de 50 anos [RR 1,13 (95% CI, 1,04-1,21) e 1,34 (95% CI, 1,04-1,71)].

Recentemente foi demonstrado aumento da frequência de disfunção eréctil, patologia marcadamente relacionada com aterosclerose, nos doentes com psoríase, apesar de não ter sido mostrado que a psoríase seria um factor de risco independente para disfunção eréctil.[14]

Este aumento de doença cardiovascular em doentes com psoríase poderá resultar de múltiplos mecanismos. Por

um lado, a elevada incidência de múltiplos factores de risco de doença cardiovascular, como obesidade, hipertensão, dislipidemia e diabetes (provavelmente geneticamente relacionada) e, por outro, a inflamação sistémica existente na psoríase que promove uma aterosclerose precoce. (Fig. 2)

Inflamação e Aterosclerose

Está bem demonstrado que a inflamação sistémica se associa ao desenvolvimento de aterosclerose.[8] Assim, considera-se que os doentes com psoríase, especialmente os mais graves, possam ter um risco superior de doença cardiovascular.

De facto, a inflamação sistémica presente na psoríase parece promover uma aterosclerose acelerada de forma independente, através de disfunção endotelial e *stress* oxidativo, em muito semelhante à observada noutras doenças inflamatórias crónicas sistémicas como o lúpus eritematoso sistémico.[15]

Na psoríase, a inflamação caracteriza-se por elevados níveis de TNF-α, INF-γ, INF-α, IL-1, IL-6 e IL-17, produzidos pelas células inflamatórias que infiltram a pele (linfócitos, neutrófilos e células dendrítica) e pelos queratinócitos ativados.[3] Estas citoquinas têm a capacidade de induzir várias funções pró-aterogénicas do fígado e tecido adiposo, incluído a produção de proteína C reactiva e outras adipoquinas pró-inflamatórias conduzindo a insulino-resistência e disfunção endotelial.[16]

A inflamação aterosclerótica assemelha-se à observada na psoríase, incluindo o perfil de citoquinas e os tipos de células imunológicas intervenientes (ambas as patologias são principalmente mediadas por linfócitos Th1).[8] Na psoríase, tal como na aterosclerose ocorre uma desregulação entre Th17 / Treg (linfócitos T reguladores), com aumento da expressão de citoquinas dependentes dos Th17 por diminuição dos Treg.[17]

O impacto clínico tem vindo a ser demonstrado em vários estudos, que demonstraram um aumento da prevalência de aterosclerose em doentes com psoríase. Ludwig et al[18] mostrou maior prevalência de calcificação arterial coronária em doentes com psoríase, demonstrando igualmente que a psoríase seria um factor de risco independente para calcificação arterial coronária. Muitos outros indicadores de aterosclerose, como a espessura da íntima-média da artéria carotídea, rigidez arterial ou disfunção endotelial mostraram estar consistentemente aumentados nos doentes com psoríase especialmente nos mais graves, comparativamente com o grupo controlo, observando-se na maioria dos casos correlação com o grau de inflamação.[19-21] (Fig. 3)

COMORBILIDADES CARDIOVASCULARES

Hipertensão arterial

A presença de prevalência aumentada de HTA em doentes com psoríase comparativamente com outros doentes dermatológicos já foi demonstrada em vários estudos.[4,22-24] Uma recente meta-análise de estudos observacionais demostrou que os doentes com psoríase apresentam um risco

Figura 2 – Lesão característica de psoríase: placa eritematosa, bem delimitada recoberta por descamação branca-prateada; Fenótipo comum a vários doentes com psoríase grave: envolvimento superior a 10% da superfície corporal por placas de psoríase, obesidade central e presença de vários factores de risco cardiovasculares como hipertensão arterial, dislipidemia ou diabetes mellitus.

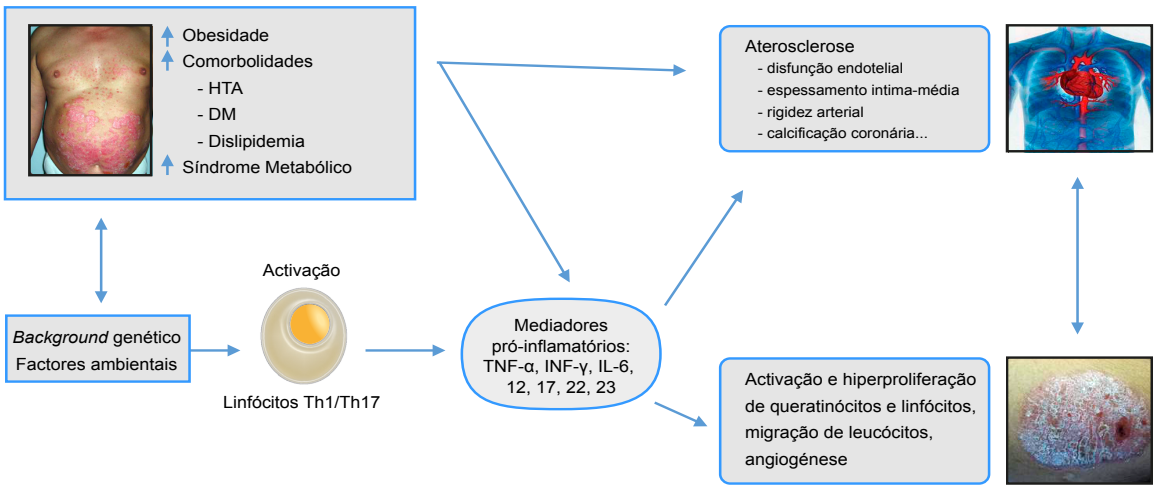

Figura 3 – Relação entre psoríase, inflamação, comorbilidades cardiovasculares e doença cardiovascular [Adaptado de Flammer AJ, Ruschitzka F.Psoriasis and atherosclerosis: two plaques, one syndrome? Eur Heart J. 2012;33:1989-91.]

1,58 vezes superior do que a população geral de ter HTA. Adicionalmente, a psoríase grave parece conferir um risco acrescido relativamente aos casos ligeiros (OR 1,49; 95% CI, 1,20-1,86 *vs* OR 1,30; 95% CI 1,15-1,47).[24] A maioria dos estudos mostrou ainda uma associação independente entre HTA e psoríase após ajuste a múltiplos factores confundidores, como a idade, sexo, obesidade e tabaco.[24]

A razão está ainda por esclarecer, mas foram observados em doentes com psoríase, níveis aumentados da enzima conversora de angiotensina e da actividade da renina, que têm como funções regular o tónus vascular e estimular a libertação de citoquinas pró-inflamatórias,[25,26] assim como de endotelina-1, um potente vasoconstritor que poderá contribuir em parte para a prevalência aumentada de HTA em doentes com psoríase.[24]

Resistência à insulina/Diabetes mellitus

Múltiplos estudos sugerem a possível associação entre psoríase e o aumento dos níveis séricos de glicose, hiperinsulinémia, resistência à insulina e DM tipo 2.[27-29] Neimann et al[4] observou uma prevalência de DM de 7,1% em doentes com psoríase grave comparativamente com 3,3% no grupo controlo. Quereshi et al[30] mostrou que a psoríase estava independentemente associada com DM (RR = 1,63), enquanto o OR de desenvolver DM era de 2,56 e que o risco se correlacionava com a gravidade da psoríase. Além disso, vários trabalhos mostraram que a prevalência aumentada de DM nos doentes com psoríase seria independente de factores de risco tradicionais de DM, como a dislipidemia e obesidade,[31-33] apesar de se saber que a obesidade e especialmente a obesidade abdominal está fortemente associada ao desenvolvimento de síndrome metabólico e DM tipo 2.

Os mecanismos potenciais para esta relação permanecem ainda um pouco por esclarecer. Boehncke et al[34] mostrou uma associação significativa entre a gravidade da psoríase, a secreção de insulina e níveis séricos de resistina, citoquina aumentada em estados de resistência à insulina. Por outro lado é conhecido o papel do TNF-α, uma das principais citoquinas pró-inflamatórias na psoríase, na regulação da função da insulina. A indução de resistência à insulina pelo TNF-α poderá acontecer, pelo menos em parte, pelo seu efeito a nível dos adipócitos e hepatócitos.[35] Assim, a resistência à insulina observada nos doentes com psoríase grave poderia, em parte, ser devida à inflamação crónica sistémica observada nestes doentes, conceito cada vez mais aceite.[4] Adicionalmente, estudos genéticos revelaram uma associação entre *loci* de susceptibilidade de DM e de psoríase.[36]

Dislipidemia

Vários estudos observacionais e caso-controlo têm demonstrado uma associação entre psoríase e dislipidemia aterogénica, mesmo quando ajustados à idade, sexo e obesidade.[4,23,37-39] Os doentes psoriáticos têm concentrações plasmáticas mais elevadas de triglicerídeos, colesterol total, VLDL, LDL e lipoproteína A e igualmente concentrações séricas baixas de HDL e apolipoproteína B.[37,40-42]

Interessante é também a demonstração que este perfil dislipidémico se encontra presente desde o início da doença cutânea (< 1 ano) sugerindo que a dislipoproteinémia possa ser determinada geneticamente em vez de adquirida. Adicionalmente, foi demonstrado estar presente em doentes com psoríase em placa e gutata um polimorfismo genético da apolipoproteína E, fortemente associada com estados dislipidémicos.[43] Contudo, apesar da existência de estudos genéticos que associem estas patologias, a relação fisiopatológica entre elas não foi ainda totalmente esclarecida, mas provavelmente está relacionada com a produção aumentada de citoquinas pro-inflamatórias, principalmente o TNF-α, a leptina e a IL-6, observada nos doentes com psoríase, que têm um papel importante na regulação dos níveis de lípidos, ácidos gordos livres e colesterol.[44-46]

Obesidade

A obesidade é uma comorbilidade frequente na psoríase e vários estudos têm demonstrado que estes doentes têm mais frequentemente excesso de peso (IMC ≥ 25 kg/m^2 e < 30 kg/m^2) e obesidade (IMC ≥ 30 kg/m^2) quando comparados com uma população sem psoríase.[4,22-23,40] Neimann et al[4] observou que a prevalência da obesidade em doentes com psoríase grave era de 20,7% quando comparada com 13,2% do grupo controlo. Num ensaio clinico com etanercept com 3 700 doentes a prevalência de obesidade foi de 46%. Além disso, o IMC médio em 10 000 doentes com psoríase moderada a grave que participaram em ensaios clinico foi de 30,6 kg/m^2.[47]

Num estudo populacional recente em doentes com psoríase ligeira e grave, observou-se que o risco de obesidade nos doentes psoriáticos era significativamente maior comparativamente com o grupo controlo e que se associava com a gravidade da doença (OR 1,27; 95% CI, 1,24-1,31; e OR 1,79; 95% CI, 1,55-2,05 para doença ligeira e grave respectivamente).[4]

Apesar de haver uma forte associação entre obesidade e psoríase, é ainda controverso se a obesidade é causa ou consequência de psoríase e a etiologia desta ligação permanece ainda incerta. Sabe-se que nos doentes obesos existe um aumento dos mediadores inflamatórios, semelhantes aos encontrados na resposta inflamatória mediada por células Th1.[48] Assim, acredita-se que as citoquinas produzidas na pele possam actuar directamente sobre o tecido adiposo e vice-versa. Esta hipótese é corroborada por níveis aumentados de proteína C reactiva, TNF-α, IL-2 e IL-6, encontrados nas duas patologias.[48,49] O TNF-α leva a hiperinsulinémia através da resistência à insulina, fazendo com que as células endoteliais produzam moléculas de adesão aos monócitos, assim como reduz a síntese de adiponectina, prejudicando a sinalização da insulina. Estes elementos comuns estão envolvidos nas fases iniciais da inflamação. Deste modo, a obesidade pode potenciar a inflamação da psoríase, e simultaneamente, facilitar o desenvolvimento de síndrome metabólico.[49]

Existe igualmente evidência que a perda de peso tem efeito na eficácia das terapêuticas usadas no tratamento da psoríase, assim como na gravidade da doença, provavelmente por diminuir a inflamação sistémica.[50]

Síndrome Metabólico

A síndrome metabólica refere-se a um conjunto de factores de risco de doença cardiovasculares, que quando presentes no mesmo doente aumentam o risco cárdio-metabólico. Os indivíduos com esta síndrome têm um aumento de 3 a 9 vezes do risco de desenvolver diabetes tipo II, de 2-3 vezes de eventos cardiovasculares (EAM, AVC) e de 1,5 vezes de mortalidade cardiovascular.[51]

Entre os vários critérios de diagnóstico de síndrome metabólico, o National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) é o mais utilizado nos EUA e na Europa, e define a síndrome metabólico como a presença de três ou mais dos seguintes componentes: obesidade abdominal (circunferência da cintura ≥ 102 cm em homens, ≥ 88 cm em mulheres), aumento da resistência à insulina / elevada glicemia em jejum (≥ 100mg/dL, ou em tratamento), diminuição da lipoproteína de alta densidade (< 40 mg/dL em homens, < 50 mg/dL em mulheres, ou em tratamento), hipertrigliceridémia (≥ 150 mg/dL, ou em tratamento) e hipertensão arterial (pressão arterial sistólica ≥ 130 mmHg, ou diastólica ≥ 85 mmHg, ou em tratamento).[52]

Os doentes com psoríase têm um risco aumentado de síndrome metabólico e dos seus componentes individualmente. Por exemplo, comparando uma população de doentes com psoríase grave com uma população controlo internada para cirurgia de melanoma em fase inicial observou-se que o risco de desenvolver síndrome metabólico era significativamente superior nos primeiros (OR de 5,92; 95% CI, 2,78 - 12,8).[24]

A obesidade abdominal e a resistência à insulina são consideradas factores de risco subjacentes ao desenvolvimento de síndrome metabólico. Além disso, esta síndrome está também associada a um estado pró-inflamatório e pró-trombótico, que consiste em níveis elevados de IL-6, TNF-α, leptina, inibidor de activador de plasminogénio (PAI-1), fibrinogénio e proteína C reactiva, e diminuição dos níveis de anti-inflamatórios, como a adiponectina. Como referido anteriormente, entre as citoquinas inflamatórias, o TNF-α desempenha um papel crucial quer na psoríase, quer na síndrome metabólico.[53-56]

A leptina parece ter um papel central nesta ligação. Independentemente da obesidade e da síndrome metabólico, observou-se nos doentes com psoríase hiperleptinemia. Além disso, observou-se nos doentes com psoríase graves níveis séricos elevados de leptina e do receptor cutâneo da leptina.[16,57]

Tabagismo

Vários estudos têm demonstrado que o tabagismo é mais prevalente nos doentes psoriáticos comparativamente aos restantes doentes.[58-61] A razão é desconhecida mas poderá estar relacionada com o estado de ansiedade e de depressão muitas vezes associado à psoríase. A relação entre tabaco e aumento do risco de doenças cardiovasculares está bem estabelecida, contudo a ligação entre o tabaco e a psoríase necessita de fundamentação. O fumo do cigarro expõe o corpo a substâncias potencialmente tóxicas, como é o caso da nicotina, espécies reactivas ao oxigénio e óxido nítrico, que poderão estar envolvidas na patogénese da psoríase.[62]

Efeito do tratamento da psoríase no risco cardiovascular

O tratamento da psoríase com medicação sistémica poderá influenciar o risco cardiovascular dos doentes. O metotrexato mostrou reduzir o risco de eventos cardiovasculares embora esta evidência tenha sido demonstrada especialmente em estudo observacionais de doentes com artrite reumatóide. Vários estudos demonstraram que a utilização de inibidores do TNF-α melhora, a curto prazo,

alguns marcadores de risco de doença cardiovascular (por exemplo disfunção endotelial) e que a longo prazo parecem reduzir efectivamente a incidência de diabetes e de eventos cardiovasculares.[63,64]

Por outro lado, o tratamento dos factores de risco cardiovasculares, especialmente a obesidade, parece ter efeito na gravidade da psoríase, provavelmente por diminuição da inflamação associada à obesidade.[65]

CONCLUSÃO

Na última década, observou-se uma mudança drástica no conceito de doença na psoríase, deixando esta de ser vista como uma doença exclusivamente cutânea mas sim como uma doença inflamatória crónica, multissistémica, com um envolvimento muito para além da pele.

Os doentes com psoríase têm um risco aumentado de desenvolver várias comorbilidades cardiometabólicas, como hipertensão arterial, dislipidemia, resistência à insulina e obesidade, que conjuntamente com a inflamação sistémica crónica que promove uma aterosclerose precoce, é responsável pelo aumento do risco de doença cardiovascular observado nestes doentes. Esta associação a factores de risco cardiovasculares e risco aumentado de doença cardiovascular observa-se em todo o espectro de gravidade da psoríase, contudo parece ser mais importante nos doentes com psoríase grave provavelmente decorrente de um estado inflamatório mais elevado.

Embora esta associação esteja ainda por esclarecer completamente, a partilha genética e certas citoquinas pró-inflamatórias e adipocitoquinas parecem contribuir para o desenvolvimento destas comorbilidades e de doença cardiovascular.

O papel dos dermatologistas é da maior importância, não só pela possibilidade de identificar precocemente as diversas comorbilidades ou doença cardiovascular, mas também pela possibilidade de ao tratar correcta e eficazmente a psoríase e inflamação sistémica subjacente, poderem prevenir as possíveis complicações.

A abordagem destes doentes deve ser multidisciplinar, com os dermatologistas, cardiologistas, endocrinologistas e médicos de medicina geral e familiar a trabalhar conjuntamente de forma a optimizar o diagnóstico, monitorização e tratamento das diversas comorbilidades, prevenindo os eventos cardiovasculares.

Os doentes deverão ser encorajados a corrigir os factores de risco cardiovasculares modificáveis, como a obesidade, tabaco e sedentarismo e adoptarem um estilo de vida saudável, uma vez que para além de melhorarem o seu perfil cardiovascular, há hoje evidencia que tal pode resultar numa melhor resposta ao tratamento.

Por fim, são necessários estudos que permitam identificar biomarcadores analíticos e genéticos que identifiquem os doentes com psoríase em maior risco de desenvolver doença cardiovascular, no sentido de implementar medidas preventivas.

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Sem conflitos de interesse.

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Psoríase e Obesidade

Correia B, Torres T. Obesity: a key component of psoriasis. (submetido)

Obesity: a key component of psoriasis

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Obesity: a key component psoriasis

Abstract

Psoriasis has been associated with several cardiometabolic comorbidities and with clinically significant increased risk of cardiovascular disease and cardiovascular mortality. Obesity seems to have a key role linking psoriasis and cardiovascular disease as there is a growing number of epidemiological studies associating psoriasis and obesity.The mechanism responsible for the association between these two conditions is not certain, but it is probably multifactorial, with genetic, environmental and immune-mediated factors having a role. The chronic inflammatory state associated with obesity seems to be a key component of this relationship. For this reason, obesity is a major factor in the management of psoriatic patients, with implications in treatment efficacy and safety. Moreover, weight loss has been shown to improve psoriasis severity and response to treatment. The aim of this review is to synthesize the current literature on the association between psoriasis and obesity, to explore the physiopathological mechanisms that link both diseases and to highlight the importance of obesity control in the efficacy and safety of systemic treatment of psoriasis. It is essential that all clinicians are aware of this association, so they can recognize it and provide the patients a proper follow-up and multidisciplinary approach when needed.

Key-words

Psoriasis, obesity, systemic inflammation, cardiometabolic comorbidities, cardiovascular disease, adipokines, adipocytes

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease affecting 1.5 to 3% of the world's population[1]. Disease onset can occur at any age, however generally there are two peaks of onset, the first at 20-30 years and the second at 50-60 years. Men and women are equally affected, and there is higher prevalence in Caucasians compared with African Americans[2,3].

Patients with psoriasis present a range of clinical manifestations, that go from limited disease to very extensive disease. It is characterized by erythematous, scaling plaques and concurrent symptoms such as burning or itching of the skin, affecting the nails in 35 to 50% of cases[4,5]. Furthermore, quality of life impairment and increased social and economic costs to both patients and health care systems are still concerning issues around the management of the disease[6,7]. In the past years, several epidemiological studies have shown that psoriasis is associated with multiple comorbidities, particularly cardiovascular/metabolic diseases, such as hypertension, diabetes *mellitus* type II, dyslipidemia and obesity[8]. Moreover, it has also been suggested that it is linked to a higher risk of cardiovascular mortality, specially within patients with greater disease severity, possibly due to the concomitant systemic inflammation[9-11]. Obesity seems to have a central role, as it is often strongly associated with these cardiovascular risk factors.

The precise mechanism linking these two conditions is not certain, but it is probably multifactorial, with genetic, environmental and immune-mediated factors playing a role, and the chronic inflammatory state of obesity being a key component of this association[12]. Thus, obesity is nowadays considered to be a major factor on the management of psoriatic patients[13,14].

The objective of this review is to synthesize the current literature on the association between psoriasis and obesity, to explore the physiopathological mechanisms that link both diseases and to highlight the importance of obesity control in the efficacy of systemic treatment of psoriasis, as it is essential that all medical doctors recognize the presence of these comorbidities in psoriatic patients, in order to improve their screening and management.

Obesity and psoriasis: current evidence

The association between psoriasis and obesity has been the focus of several epidemiologic studies and review articles over the last years[15]. Lindegård first described this association in 1986, as the result of a study of 159,200 Swedish citizens over a 10-year period, reporting a higher prevalence of obesity in women with psoriasis than in the female general population[16]. Also, in 1995 Henseler and Christophers concluded that obesity was one of the systemic disorders that often affected psoriatic patients, analyzing data from 40,000 patients[17].

More recently, a growing number of studies confirmed this association, demonstrating that patients with psoriasis are more frequently overweight (Body Mass Index (BMI) 26 – 29 kg/m^2) or obese (BMI ≥ 30 kg/m^2) when compared with patients without psoriasis[18-20]. Some cross-sectional studies even noted that the increase in BMI is related to a greater degree of psoriasis disease severity[20,21].

In an Italian case-control study with 560 psoriatic patients, obesity was found to be an independent risk factor for the development of psoriasis, as the odds ratio (OR) of having psoriasis were 1.6 (95% CI, 1.1-2.1) and 1.9 (95% CI, 1.2-2.8) for overweighted and obese patients, respectively, compared to non-obese control individuals[18]. A population-based study from the UK consisting of 127,706 patients with mild psoriasis and 3,854 patients with severe psoriasis demonstrated higher adjusted odds of obesity in patients with severe disease (OR 1.84; 95% CI, 1.60-2.11) than in patients with mild disease (OR 1.3; 95% CI, 1.26-1.32) compared with patients without psoriasis[21]. In another study, with a sample of 16,851 patients with psoriasis and 48,681 controls, obesity was present in 8.4% of the psoriatic patients as opposed to 3.6% of controls ($p<0.001$). Moreover, after multivariate adjusting for age and other confounders, patients younger than 35 years old were more likely to be obese (OR 2.2; 95% CI, 1.7-2.7) than patients older than 65 years old (OR 1.6; 95% CI, 1.4-1.8), compared with normal controls[19].

In 2012, a systematic review and meta-analysis of observational studies concerning the association between psoriasis and obesity was published. 16 observational studies were selected and a total of 2.1 million study participants (201 831 psoriatic patients) fulfilled the inclusion criteria. The pooled OR for obesity among psoriatic patients was 1.66 (95% CI, 1.46-1.89) compared with those without psoriasis. Regarding psoriasis

severity, the pooled OR for obesity among patients with mild psoriasis was 1.46 (95% CI, 1.17-1.82) and the pooled OR for patients with severe psoriasis was 2.23 (1.63-3.05). Reporting one incidence study, it was found that psoriatic patients have a hazard ratio of 1.18 (95% CI, 1.14-1.23) for new-onset obesity. It was concluded that psoriatic patients have higher prevalence and incidence of obesity as well as patients with severe disease have greater odds of obesity than those with mild disease[15].

Interestingly, this association appears to be present already at young age. In an international cross-sectional study, developed by Paller *et al* to investigate the relationship between excess and central obesity and psoriasis in 409 psoriatic children and 205 controls from 9 different countries, the OR of obesity (BMI above the 95th percentile) in psoriatic children versus controls was 4.29 (95% CI, 1.96-9.39), being higher in severe psoriasis (4.92; 95% CI, 2.20-10.99) than in mild psoriasis (3.60; 95% CI, 1.56-8.30). Moreover, an increased central adiposity in the psoriasis group was also found, as waist circumference and waist-to-height ratio, two non-invasive surrogates for central adiposity and more sensitive indicators for metabolic disease than BMI percentile, were significantly higher in psoriatic children than in controls[22].

This data suggests that the association between obesity and psoriasis may be in part genetically determined rather than uniquely acquired.

Inflammation: the main link between obesity and psoriasis

Once described as a skin disease derived primarily of epidermal keratinocyte proliferation, psoriasis is now seen as a dysregulation of both innate and adaptive immune system, mediated by cytokines, decisive to the initiation and maintenance of the psoriatic plaques[23]. Lymphocytes T-helper (Th)-1 and Th-17 are highly concentrated within the skin lesions and are fundamental to disease expression, producing several inflammatory cytokines such as interferon (IFN)- γ, tumor necrosis factor (TNF)- α, IL-2, IL-6, , IL-17 and IL-22, essential to keratinocyte activation and proliferation[24-26]. Keratinocytes produce autocrin growth factors and cytokines (TNF-α, IL-1, IL-6, IL-8, IL-15, IL-20) that lead to further epidermal hyperplasia and recruitment of T-cells, thus sustaining and amplifying the inflammatory responses and the psoriatic lesions[27,28] (Fig. 1).

(Insert Figure 1 here)

Also, obesity is nowadays considered a low grade chronic inflammatory disease, as several pro-inflammatory cytokines and adipokines are systemically increased. This inflammatory activity of adipocytes can partially explain the association between psoriasis and obesity[29,30].

Indeed, adipose tissue is currently considered an active immune and endocrine organ taking part in a variety of metabolic functions[31]. Within adipose tissue, there is evidence of an accumulation of activated inflammatory-type macrophages, that stimulates the secretion of inflammatory mediators by adipocytes, thus perpetuating the inflammatory state (TNF-α, IL-6, M-CSF -macropaghe colony-stimulating factor, MCP-1 – monocyte chemoattractant protein-1)[32]. Many of these cytokines play a role in psoriasis inflammatory pathways. Adipocytes, especially those in visceral adipose tissue, produce a group of bioactive substances, named adipokines, that present endocrine, paracrine and autocrine activity and also hold pro-inflammatory, thrombotic and vasoactive properties[31]. The relationship between adipokines and the establishment of metabolic syndrome lies within their participation in several proatherogenic processes, as they can induce obesity, insulin resistance, dyslipidemia, hypercoagulability, inflammation and endothelial dysfunction[33]. Different actions characterize the existing wide range of adipokines. An increase in pro-inflammatory adipokines (such as leptin and resistin) is seen in psoriasis, however, a decrease in regulatory adipokines (like adiponectin) is also noted[34,35].

Leptin is produced primarily by adipocytes. Beyond regulating appetite and body weight, through the transmission of afferent signals of the nutritional and fat mass status to the hypothalamus, leptin has influence in many other metabolic processes including neuroendocrine function, hematopoiesis and immune responses. It participates in acute and chronic inflammatory processes by regulating cytokine expression that balances Th1 and Th2 cells, promoting the differentiation of T cells into a Th1 phenotype[36]. Leptin has been shown to stimulate angiogenesis and keratinocyte proliferation[37] and to promote macrophage activity, potentiating the production of several pro-inflammatory cytokines such as TNF-α[36]. Also, TNF-α can cause circulating levels of leptin to increase, independently from food intake[38]. On the other hand, hyperleptinemia is associated with cardiovascular conditions like arterial thrombosis and intima-media thickness of the common carotid artery[39]. One research has

suggested that high levels of leptin in obese patients can contribute to psoriasis by increasing levels of pro-inflammatory cytokines[40]. In addition, a positive correlation was found between leptin and its receptor's expression and serum levels of leptin with psoriasis severity and duration, suggesting that leptin may serve as a marker of the severity and chronicity of psoriasis[41].

Resistin is another adipokine linking psoriasis, obesity and cardiovascular disease. It is produced by monocytes and macrophages in adipose tissue and peripheral blood. It has been shown that increased resistin expression, along with the inflammation associated, can be a predictor of endothelial dysfunction and a sign for atherosclerosis. In addition, proinflammatory cytokines such as TNF-α, IL-1- β and IL-6 can increase resistin expression, which in turn upregulates the production of TNF-α and IL-12[42]. There is evidence that plasma levels of resistin are significantly increased in psoriasis and positively correlated with Psoriasis Area and Severity Index scores (PASI scores). Following psoriasis' treatment, its levels were decreased, therefore suggesting that it might be useful for evaluating disease activity[43].

Finally, adiponectin seems to be decreased in obese psoriatic patients and to be inversely correlated with psoriasis severity[44,45]. Adiponectin has an important anti-inflammatory action as it induces the secretion of IL-10 and inhibits the production of TNF-α, IL-6, IFN-γ and ICAM-1 (intercellular adhesion molecule 1)[46].

TNF-α and IL-6 are probably the most important pro-inflammatory cytokines involved in the association between psoriasis and obesity. TNF-α is produced by monocytes and macrophages, lymphocytes, mast cells, NK cells and keratinocytes and is a key cytokine in psoriasis pathogenesis, being overexpressed in lesional skin and serum of psoriatic patients[47]. In obese patients, TNF-α is believed to be mainly produced by the macrophages of stromal and vascular adipose tissue. TNF-α mRNA and TNF-α protein were found to be 2.5 and 2 times higher, respectively, in adipocytes of obese patients compared to normal-weight controls[48]. In addition, TNF-α expression in adipocytes of obese patients decreases when the patient undergoes a weight loss process[49]. There is evidence of higher levels of circulating TNF-α receptors in obese patients[50]. Besides contributing to insulin resistance, TNF-α increases its own production and that of leptin, IL-6, resistin, and MCP-1, while it down-regulates the levels of adiponectin[51].

Concerning IL-6, its systemic levels have been found to be increased in psoriasis, particularly in patients with severe disease[52] and IL-6 is one of the main mediators of the chronic inflammatory state that represents obesity, as adipocytes and macrophages are involved in its production. Around 30% of circulating IL-6 is produced in stromal adipose tissue and the expression of IL-6 directly correlates with BMI and adipose tissue[53] Furthermore, IL-6 is linked to insulin resistance and diabetes *mellitus* type II[54], being a possible link between psoriasis, obesity and cardiovascular disease.

The bidirectional relationship between obesity and psoriasis: which comes first?

The discussion around what is the predisposing factor is a common question. However, the relationship between obesity and psoriasis is probably bidirectional.

Several mechanisms have been proposed to explain why psoriasis might lead to obesity, including decreased physical activity, increased social isolation, depression, unhealthy dietary habits and increased alcohol consumption. In fact, in a case-control study it was found that both male and female psoriatic patients consumed more total fat, saturated fat and alcohol than the respective healthy controls[55]. Recently, it has been shown that psoriatic patients exhibit decreased levels of physical activity comparing to the general population[56].

On the other hand, there is also evidence indicating that obesity may predispose patients to the development of psoriasis. In a study involving 78,626 women (of whom 892 reported having psoriasis), it was shown that increased adiposity and weight gain was associated with greater risk of developing psoriasis, with the incidence of psoriasis being linearly correlated with the BMI[57]. Probably, the inflammatory nature of obesity and the enhanced secretion of pro-inflammatory cytokines and adipokines by visceral fat, that play a role in the psoriasis pathogenesis, may predispose the development of psoriasis in genetically susceptible patients.

Impact of obesity on the management of psoriatic patients

Obesity has several implications in the management of psoriatic patients. There is evidence that obesity decreases the response to systemic and biologic therapies, that obese patients are at greater risk of adverse effects and that weight loss might improve the response to therapy.

Increased body weight and BMI are associated with decreased response to systemic therapies, mainly those with fixed dose regimens[58]. In an Italian cohort study, that analyzed the role of BMI in the clinical response to systemic treatment for psoriasis, it was found that BMI was a predictor of treatment response, with PASI 75 response rate being inversely correlated with increasing BMI[59].

Several studies have compared the therapeutic efficacy of fixed versus adjusted dosed biologic therapies in obese patients. Fixed dosed regimens of biologic drugs are often associated with a compromised efficacy in heavier patients, as the studies showed an evident relationship between increasing BMI and decreasing response rates in clinical trials[60]. This means that body weight is a factor that should be considered in the choice of therapeutic regimen, as adjusting the dose of these biologic drugs according to weight can optimize effectiveness and avoid excessive doses in patients with lower weight.

Another important issue concerns the increased risk of adverse effects to systemic treatments associated with obesity. Methotrexate hepatotoxicity may be increased in obese psoriatic patients due to nonalcoholic steatohepatitis, a comorbid condition usually associated with obesity[61]. Moreover, it has been demonstrated that obesity may be a greater risk factor for hepatotoxicity than alcohol or viral hepatitis in patients with psoriasis treated with methotrexate, particularly when associated with other risk factors like diabetes *mellitus*[62]. For this reason, obesity is considered by some authors to be a relative contraindication to this treatment[61]. Regarding cyclosporine, caution is required in obese patients, since serum levels of the drug are paradoxically high in this group, increasing the risk of nephrotoxicity[63].

On the other hand, weight loss is crucial to improve the response to therapy in obese psoriatic patients with moderate to severe disease, probably due to the reduction of the inflammatory burden. Besides, it also decreases the risk of toxicity and enhances effectiveness of therapies[64]. The first reports of psoriasis improving with weight loss and caloric reduction date back to malnourished prisioners during World War II[65]. Furthermore, in a trial of 82 patients with psoriasis, Rucevic *et al* demonstrated that those randomized to a low-calorie, low-fat diet for 4 weeks had a greater, and statistically significant, improvement of their psoriasis, compared to patients randomized to undergo a standard hospital diet, along with reduction in levels of their

total cholesterol, triglycerides and low-density lipoproteins[66]. Moreover, in another study, undergoing a low-calorie diet improved the response of obese patients with moderate to severe chronic plaque psoriasis to low-dose cyclosporine therapy[67]. Finally, there are several isolated cases and small series relating gastric bypass surgery and the consequent weight loss to improvement of psoriasis severity, probably due to the decrease of the inflammatory state associated with obesity[68-70]. Further investigation is underway to establish the role of this therapy in the management of psoriasis[71].

Conclusion

There is strong evidence of an association between obesity and psoriasis and, as shown before, this has several implications in psoriasis management. There are several factors that may be implicated in this association, such as genetic, environmental or immune-mediated, but special focus should be given to the obesity associated chronic inflammatory state, which plays a key role in the physiopathologic pathways that link the two conditions.

Dermatologists have an important role in the management of these patients, as they are often the only physicians dealing directly with them. It is essential that they screen these patients for comorbidities and refer to other specialties when needed, in order to obtain a multidisciplinary approach. However, it is also crucial that all the other clinicians are aware of this association so they can recognize it and provide a proper follow-up.

Clinicians should take into consideration the efficacy and safety issues affected by obesity when deciding the proper treatment for psoriatic patients and should encourage patients to adopt healthy lifestyle behaviors, such as healthy eating habits, physical activity and smoking cessation as well as weight loss, as all these measures can affect positively the prognosis of patients with psoriasis.

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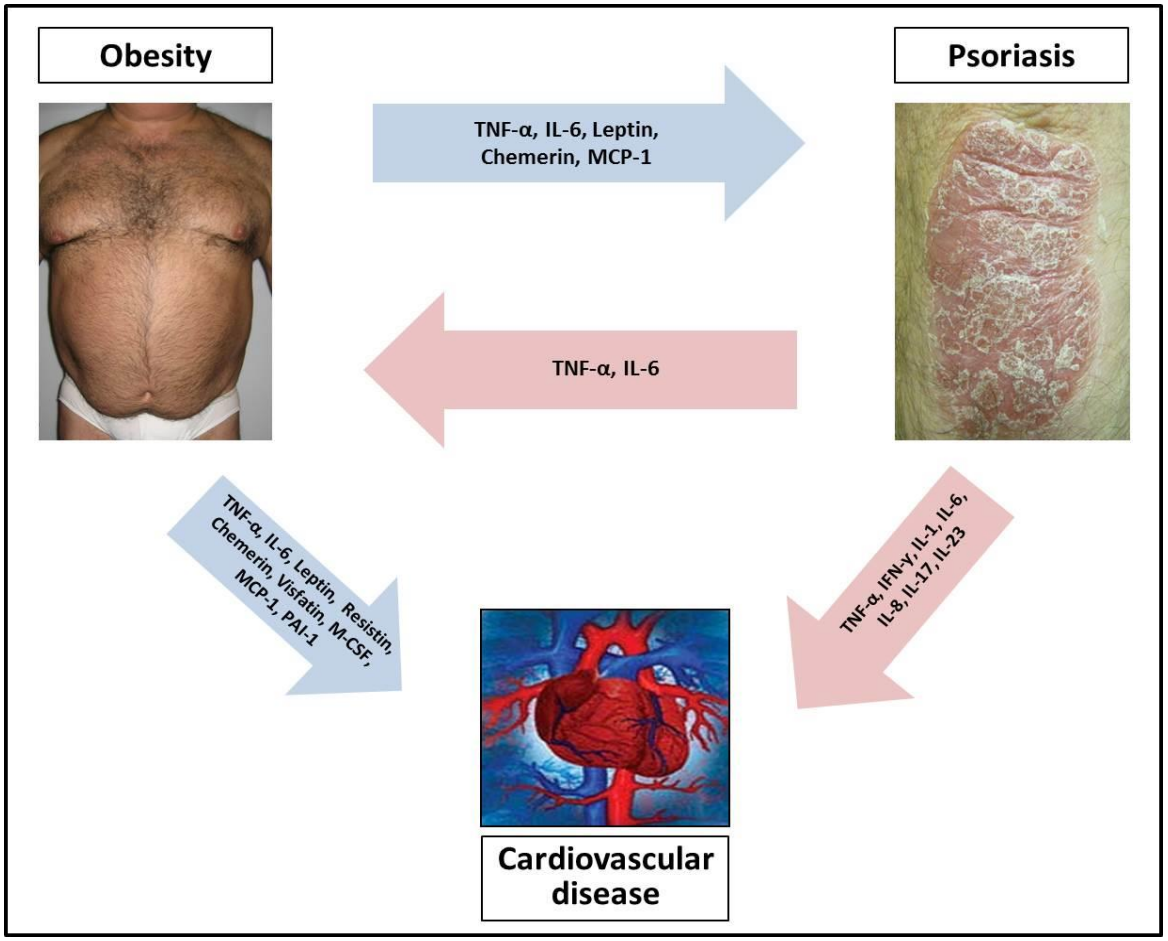
Figure 1 – Inflammatory mediators associating obesity, psoriasis and cardiovascular disease.



Psoríase e Síndrome Metabólico

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Psoriasis and metabolic syndrome

Short title: Psoriasis and metabolic syndrome

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ABSTRACT

Psoriasis is a chronic, systemic inflammatory disease associated with several cardiometabolic comorbidities, such as obesity, insulin resistance, dyslipidemia and hypertension, and with clinically significant increased risk of cardiovascular disease and cardiovascular mortality. These comorbidities are components of the metabolic syndrome. Multiple epidemiologic studies have revealed a high prevalence of metabolic syndrome in patients with psoriasis compared with other skin diseases. Genetic susceptibility and overlapping inflammatory pathways may be potential biologic links underlying this association. Understanding the interrelationship between these conditions is important for the management of psoriasis and its associated comorbidities. This review will focus on the range of these comorbidities, emphasis on the metabolic syndrome, aiming to encourage physicians to screen these patients for cardiometabolic disorders and risk factors.

Key words: metabolic syndrome, psoriasis, cardiovascular disease, atherosclerosis, insulin resistance

1. INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease that affects 1% to 3% of the general population (1). It affects both sexes equally and people of all ages, with incidence peaks in early adult life (20s) and later adult life (50s and 60s) (2, 3). It is clinically characterized by sharply demarcated erythematous plaques covered by silvery-white scales preferentially at the elbows, knees, scalp, umbilicus and lumbar area, and histologically by epidermal hyperplasia, dilatation and proliferation of dermal blood vessels and accumulation of inflammatory cells, particularly neutrophils and T lymphocytes in the dermis (4). Both genetic and environmental factors are involved in its pathophysiology (5-7).

Although rarely life threatening, psoriasis has a similar negative impact on patients' quality of life to that of patients living with diabetes, cancer or heart disease (8), a fact well reported by most patients. More than skin deep, psoriasis is nowadays considered a systemic inflammatory disorder (9) associated with numerous medical comorbidities and with clinically significant increased risk of cardiovascular disease (CVD) and cardiovascular mortality (10-13). The increased inflammatory load of psoriasis may play an important role in the accelerated atherosclerosis observed in these patients (14), as inflammatory processes play a key role in atherogenesis, including infiltration of inflammatory cells into the arterial intima and secretion of cytokines (15). Due to this higher incidence of cardiovascular disease, life expectancy in severe psoriasis is reduced up to 5 years (16).

2. METABOLIC SYNDROME

"Syndrome X" was the term proposed by Reaven, in 1988, for the combination of hyperinsulinemia, hypertension, glucose intolerance, high triglycemia and low high-density lipoprotein (HDL) cholesterol (17). A year later, Kaplan used the term "The deadly quartet" adding another component, upper body obesity to the constellation of hypertension, glucose intolerance, high triglycemia (18). In 1991, DeFronzo proposed the term "Insulin resistance syndrome", characterized by the combination of obesity, hypertension, lipid abnormalities, non-insulin-dependent DM and atherosclerotic cardiovascular disease (19). Lamarche called "The atherogenic metabolic triad" to the combination of high apolipoprotein B levels, high small, dense low-density lipoprotein (LDL) and hyperinsulinemia (20). Finally, the World Health Organization designated "Metabolic Syndrome" in 1999, to a cluster of risk factors that includes central obesity, atherogenic dyslipidemia, hypertension and glucose intolerance (21).

Metabolic syndrome affects approximately 15% to 25% of the general population (22, 23) and is considered a strong predictor of cardiovascular disease, diabetes and stroke (24, 25). The

combination of all its components confers a significant greater risk for development of cardiovascular disease than the attributable risk of each individual component risk factor.

There are several diagnostic criteria for metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) is widely used in the USA and Europe, and defines the metabolic syndrome as the presence of 3 or more of the following components: abdominal obesity (waist circumference ≥ 102cm in men, ≥ 88cm in women), increased insulin resistance / high fasting glucose (≥ 100mg/dL, or treatment), decreased HDL (<40mg/dL in men, <50mg/dL in women, or treatment), hypertriglyceridemia (≥ 150 mg/dL, or treatment) and hypertension (systolic blood pressure ≥ 130mmHg or diastolic blood pressure ≥ 85mmHg, or treatment) (26).

Thought to arise from insulin resistance and abnormal adipose tissue function (27), it is characterized by a low-grade of pro inflammatory state with several pro-inflammatory cytokines (e.g., TNF-α, IL-6), adipokines (e.g. leptin, resitin) and non-specific measures of inflammation (e.g., C reactive protein) levels, which result as elevated when compared to those in the absence of metabolic syndrome (28).

3. PSORIASIS AND METABOLIC SYNDROME

Several recent population-based studies have suggested a relationship between psoriasis and metabolic syndrome, with psoriasis patients having an increased risk of metabolic syndrome (29-36).

Genetic susceptibility and overlapping inflammatory pathways may be potential biologic links underlying this association (37, 38). The existence of pleiotropic genetic loci (e.g., PSORS2-4, CDKAL 1 and ApoE4) has been implicated in the shared genetic susceptibility to both psoriasis and metabolic syndrome (39, 40). On the other hand, the chronic and systemic Th-1 and Th-17-mediated inflammation of psoriasis, characterized by increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, not only promotes epidermal hyperplasia in psoriasis, but also antagonizes insulin signaling, alters adipokine expression, and mediates insulin resistance and obesity (37, 38). Moreover, the chronically high levels of free fatty acids seen in both metabolic syndrome and psoriasis may lead to adipocyte dysfunction and inhibit insulin secretion and also induce apoptosis of pancreatic b-islet cells through an endoplasmic stress response (41) leading to the development of type 2 diabetes. Finally, the altered adipokine expression and function described in psoriasis may also explain the association between psoriasis and metabolic syndrome. For instance, the leptin's antiapoptotic properties on the b-islet cells seem to be reduced in obese psoriasis patients. Thus, the

combined dysfunction of leptin, adiponectin, resistin and visfatin described in psoriasis may account for the development of metabolic syndrome and other conditions associated with atherosclerosis seen in patients with psoriasis (42, 43).

Several studies have reported the association between psoriasis and metabolic syndrome (table I).

Sommer et al. (33) showed, in a cross-sectional study with 581 hospitalized psoriasis patients and 1044 controls, that psoriasis patients had a significantly increased risk of metabolic syndrome than controls (OR=4.22; 95% CI=2.06-8.65). In a hospital-based case-control study, including 338 psoriasis patients and 334 patients with other skin diseases, Gisondi et al. found that the predominance of metabolic syndrome was significantly higher in the psoriasis group than in the control group (30.1% vs 20.6%; OR=1.65; 95% CI=1.16-2.35). Concerning the individual components of the metabolic syndrome, they found that the predominance of hypertrygliceridemia and abdominal obesity were also increased in psoriasis patients compared to controls, while no difference was observed between cases and controls with respect to low levels of HDL, DM and hypertension (32). A cross-sectional study conducted in Israel using the database of the Clalit Health Services, with 16.851 patients with psoriasis and 48.681 controls, disclosed a significant association of psoriasis with metabolic syndrome (OR=1.3; 95% CI=1.1–1.4) (34). In the USA, Love *et al*. reported significant increased risk of metabolic syndrome in psoriasis patients than among controls, even after adjustment for age, sex, race/ethnicity, smoking and C-reactive protein levels (OR=1.96; 95% CI=1.01-3.77) (44). In a population-base prevalence study in the United Kingdom using the Health Improvement Network database, with 4065 psoriasis patients and 40,650 control subjects, metabolic syndrome was identified in 34% of participants with psoriasis compared to 26% of controls, (OR=1.50; 95% CI=1.40-1.61), with this association persisting after adjusting for age, gender and follow up, adjusted (adj. OR=1.41; 95% CI=1.31-1.51). Moreover, psoriasis severity affected the degree of association, with metabolic syndrome seen in 32% with mild disease (adj. OR=1.22; 95% CI=1.11-1.35), 36% with moderate disease (adj. OR=1.56; 95% CI=1.38-1.76) and 40% of those with severe psoriasis (adj. OR=1.98; 95% CI=1.62-2.43). In addition, obesity, hypertriglyceridemia and hyperglycemia demonstrated dose-response association with psoriasis severity independently of other components (45). A recent meta-analysis synthetizing data from 12 studies and comprising 41,853 psoriasis patients from more than 1.4 million total participants, showed that the odds of metabolic syndrome were increased more than two-fold among patients with psoriasis when compared with matched controls or a cross-sectional comparator group (OR=2.26; 95% CI=1.70-3.01) (46).

Despite increasing evidence of this association and the importance of identifying and modifying the psoriasis associated cardio-metabolic comorbidities, it appears that clinical practical implementation is still modest.

In a large cohort of patients (n=2899) with moderate to severe psoriasis enrolled in a phase III clinical trial of ustekinumab, a high predominance of undiagnosed and undertreatment of cardiovascular risk factors was found. And even if these cardiovascular risk factors had been diagnosed, there was a high rate of failure to achieve treatment goal per published guidelines (47). Moreover, Parsi *et al*, assessed cardiovascular risk factor screening practices in patients with psoriasis among primary care physicians and cardiologists and their awareness of worse cardiovascular outcome in these patients, and less than half of the physicians screened these patients for cardiovascular risk factors per guidelines and less than half of all physicians were aware of greater major cardiovascular adverse events in patients with psoriasis compared with general population (48).

In 2008, the National Psoriasis Foundation, released screening guidelines and recommendations for treatment of cardiovascular risk factors in patients with psoriasis, based on the 2002 American Heart Association update (50). These recommendations include risk factor screening as early as age 20: hypertension (blood pressure ≥140/≥90mmHg), diabetes (fasting plasma glucose ≥126mg/dL), hyperlipidemia (fasting LDL-cholesterol ≥160mg/dL or triglycerides ≥200mg/dL), obesity (BMI≥30) and metabolic syndrome. By age 40, medical evaluation is recommended every two years of the following measurements: pulse, blood pressure with target <120/80 mmHg, body mass index with target <25 Kg/m^2 and waist circumference with target <88 cm for women and <102 cm for men. Fasting blood glucose should be evaluated at least every 5 years or every 2 years if other risk factors are present and its target should be <100 mg/dL. Fasting serum lipoprotein or total and HDL cholesterol should be evaluated at least every 5 years or every 2 years if a positive family history cardiovascular disease, diabetes or smoking habits are present. Total Cholesterol should be <200mg/dL, HDL ≥ 50mg/dL and LDL <130 mg/dL. (49). (table 2)

In addition, all psoriasis patients and particularly those with metabolic syndrome should be encouraged to lifestyle modifications including moderate alcohol intake, healthy eating habits, smoking cessation and exercising 3 times a week for 30 minutes.

4. CONCLUSION

There is increasing evidence that psoriasis is associated with metabolic syndrome.

Psoriasis should not be regarded as a simple skin condition but rather as a systemic inflammatory disease associated with several cardiometabolic comorbidities and increased risk

of cardiovascular disease. Thus, physicians should be aware of this association and look beyond the skin symptoms. It is important that patients with psoriasis are subjected to appropriate screening as part of routine medical care, that metabolic syndrome is correctly managed and that all psoriasis patients are encouraged to correct their modifiable cardiovascular risk factors, adopting healthier life-style behaviours such as regular physical activity.

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Table I. Study population characteristics and outcomes: Psoriasis and metabolic syndrome

Study	Study setting	Study design	Total no. of patients		Measure of association (95% CI)
			Control	Psoriasis	
Sommer et al (33) (2006)	Germany; inpatient (hospital charts)	Cross-sectional	1044	581 (hospitalized psoriasis pts)	OR 4.22 (2.06-8.65)
Gisondi et al (32)(2007)	Italy; outpatient (outpatient clinics)	Cross-sectional	334	338	OR 1.65 (1.16-2.35)
Cohen et al (34) (2007)	Israel	Cross-sectional	48,681	16,851	OR 1.3 (1.1–1.4)
Chen et al (50) (2008)	Taiwan; outpatient (dermatology clinics)	Case-control	81	77	OR 0.84 (0.31-2.26)
Chen et al (51) (2009)	Taiwan; outpatient (dermatology clinics)	Case-control	37	40	OR 2.40 (0.67-8.58)
Al-Mutairi et al (30) (2010)	Kuwait; outpatient (medical records)	Case-control	1835	1835	Mild psoriasis: OR 2.62 (2.09-3.28) Severe psoriasis: OR 4.93 (3.21-7.60)
Augustin et al (52) (2010)	Germany; outpatient (health insurance database)	Cross-sectional	1,310,090	33,981	OR 2.86 (2.21-3.71)
Bongiorno et al (53) (2010)	Italy; outpatient (dermatology department)	Cross-sectional	348	400	OR 3.4 (2.23-5.24)
Nisa and Qazi (54) (2010)	India; outpatient (dermatology department)	Case-control	150	150	OR 6.09 (NR)
Takahashi et al (55) (2010)	Japan; outpatient (dermatology clinic)	Case-control	154	151	OR 1.74 (0.99-3.05)
Love et al (44) (2011)	United States; outpatient (NHANES)	Cross-sectional	2385	71	OR 2.16 (1.16-4.03) AOR 1.96 (1.02-3.77)
Mebazaa et al (31) (2011)	Tunisia; outpatient (dermatology clinic)	Case-control	216	164	OR 1.39 (0.88-2.18) AOR 1.73 (1.06-2.82)
Langan et al (45) (2012)	United Kingdom; outpatient (THIN database)	Case-control	40,650	4065	OR 1.50 (1.40-1.61) Overall AOR 1.41 (1.31-1.51) Mild psoriasis: AOR 1.22 (1.11-1.35)

NHANES, National Health and Nutrition Examination Survey; pts, patients; THIN, The Health Improvement Network; AOR, Adjusted odds ratio; OR, odds ratio; CI, confidence interval; NR, not reported.

Table II. AHA recommendations for risk factor screening

Measurement	Recommendation	Target
Pulse	Evaluated at least every 2 years	
Blood pressure	Evaluated at least every 2 years	<120/80 mmHg
Body mass index	Evaluated at least every 2 years	<25 Kg/m^2
Waist circumference	Evaluated at least every 2 years	<88 cm for women; <102 cm for men
Fasting blood glucose	Evaluated at least every 5 years or every 2 years if risk factors are present	<100 mg/dL
Fasting serum lipoprotein or total and HDL cholesterol	Evaluated at least every 5 years or every 2 years if risk factors are present (a positive family history, presence of diabetes or smoking habits)	Total Cholesterol < 200 mg/dL HDL ≥ 50 mg/dL LDL: Optimal < 100 mg/dL; Near Optimal/Above Optimal 100 to 129 mg/dL; Borderline High 130 to 159 mg/dL; High 160 to 189 mg/dL; Very High 190 mg/dL and above

Importância da Abordagem Multidisciplinar dos Doentes com Psoríase

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REVIEW ARTICLE

Psoriasis: The visible killer

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KEYWORDS
Psoriasis;
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Cardiovascular risk factors;
Multidisciplinary approach

Abstract Psoriasis is a common chronic inflammatory disease associated with serious comorbidities. In recent years, increased mortality due to cardiovascular disease (myocardial infarction and stroke) has been documented in patients with severe psoriasis. Patients with psoriasis have a higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidemia and obesity, but it has been suggested that the chronic inflammatory nature of psoriasis is also a contributing and potentially an independent risk factor for the development of cardiovascular disease.

The authors highlight the need for early identification and treatment of psoriasis-related comorbidities and cardiovascular disease, as well as effective treatment of psoriasis, in order to reduce the underlying systemic inflammation, and also the importance of a multidisciplinary approach of severe psoriasis patients to optimize the diagnosis, monitoring and treatment of various comorbidities, so as to prevent cardiovascular events.

PALAVRAS-CHAVE
Psoríase;
Doença cardiovascular;
Aterosclerose;
Inflamação;
Fatores de risco cardiovasculares;
Abordagem multidisciplinar

Psoríase: o «assassino visível»

Resumo A psoríase é uma doença inflamatória crónica, comum, associada a comorbilidades importantes. Nos últimos anos tem sido demonstrado que os doentes com psoríase grave têm um risco aumentado de mortalidade por doenças cardiovasculares, como enfarte agudo do miocárdio ou acidente vascular cerebral. Por um lado os doentes com psoríase têm uma prevalência aumentada de fatores de risco cardiovasculares como diabetes, hipertensão, dislipidemia e obesidade, e por outro, a natureza inflamatória da doença parece contribuir e ser um fator de risco independente para o desenvolvimento de doença cardiovascular.

Os autores pretendem alertar para a necessidade da identificação precoce e tratamento das diversas comorbilidades associadas à psoríase e doença cardiovascular, assim como o tratamento

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correto e eficaz da psoríase, diminuindo a inflamação sistémica subjacente, e para a importância de uma abordagem multidisciplinar na tentativa de otimizar o diagnóstico, monitorização e tratamento das diversas comorbilidades, prevenindo os eventos cardiovasculares.

Psoriasis is a common chronic inflammatory skin disease that affects 1%–3% of the general population.[1] It affects both sexes equally and people of all ages, with incidence peaks in early adult life (20s) and in later adult life (50s and 60s).[2,3] Usually it is clinically distinct and consequently easy to diagnose, being characterized by sharply demarcated erythematous plaques covered by silvery-white scales preferentially on the elbows, knees, scalp, umbilicus and lumbar area.[4] The majority of patients, approximately 80%, have limited disease (<10% body surface area), but approximately 20% have more extensive skin involvement (>10% body surface area).[5] Although psoriasis is rarely life-threatening, its psychological impact on patients' quality of life is similar to that for diabetes, cancer or heart disease.[6] However, while most patients report its negative impact on their quality of life, psoriasis appears to be more than skin deep. As understanding of its pathophysiology has evolved, from a disorder of keratinocytes to dysregulation of the immune system mediated by cytokines, psoriasis has come to be considered a systemic inflammatory disorder associated with numerous medical comorbidities.[7]

Large epidemiologic studies have found that patients with psoriasis have a higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, smoking, obesity and metabolic syndrome compared with the general population.[8–12] Importantly, even after adjusting for these risk factors, psoriasis has been associated with clinically significant increased risk of cardiovascular disease (myocardial infarction [MI] and stroke) and cardiovascular mortality[13–20] (Table 1). For this reason, patients with severe psoriasis appear to have a 6-year reduction in life expectancy.[21]

In a study including more than 130 000 patients with psoriasis, Gelfand et al. found that the adjusted relative risk (RR) of MI in 30-year-old patients with mild psoriasis compared with controls was 1.29 (95% confidence interval [CI], 1.14–1.46), but rose to 3.10 (95% CI, 1.98–4.86) in severe forms of the disease.[16] Remarkably, the risk persisted after adjustment for major risk factors for MI, suggesting that psoriasis itself confers an independent risk of MI. Using the same database, the authors observed that patients with severe psoriasis had an increased risk of cardiovascular mortality (defined as mortality caused by MI, stroke, or peripheral vascular disease) that was independent of traditional risk factors (hazard ratio [HR] 1.57; 95% CI, 1.26–1.96). The relative risk of cardiovascular mortality was modified by age, with a higher RR in younger individuals (2.69 for 40-year-olds [95% CI, 1.45–4.99] and 1.92 for 60-year-olds [95% CI, 1.41–2.62]), suggesting a process of accelerated cardiovascular disease in younger severe psoriasis patients.[17] The authors also estimated that severe psoriasis confers an additional 6.2% absolute risk of 10-year major adverse cardiac events compared to the general population, with important therapeutic implications for cardiovascular risk stratification and prevention in patients with severe psoriasis.[18]

Psoriasis appears to be an independent risk factor for subclinical atherosclerosis, as an increased prevalence of subclinical atherosclerosis, diagnosed using various surrogate markers including carotid artery intima-media thickness, arterial stiffness, flow-mediated dilatation and nitroglycerin-induced dilatation or aortic elasticity, has been reported in several studies comparing with non-psoriatic populations, controlled for age, gender and traditional cardiovascular risk factors.[22–24] Psoriasis has also been associated with significantly increased frequency of coronary artery calcification in a study that matched patients for age, gender and known cardiovascular risk factors, not only identifying psoriasis as an independent risk factor for coronary artery calcification but also demonstrating the systemic nature of the disease.[25]

The connection between psoriasis and atherosclerosis may be due to a common genetic basis, an increased prevalence of traditional cardiovascular risk factors, and the chronic inflammation that occurs in patients with psoriasis, as inflammation has a central role in both diseases (Figure 1). Psoriasis is nowadays considered a T-cell mediated disease rather than a keratinocyte disease, and the role of T cells in the pathology of the disease demonstrates the extent of systemic involvement. Th-1, Th-17 and Th-22 cell populations are expanded and stimulated to release inflammatory cytokines, including TNF-α, IL-17 and IL-22.[26] Thus the inflammation that drives psoriatic pathology is systemic, and there is evidence that it contributes to immunologic and metabolic changes that aggravate and perpetuate psoriasis as well as to the development of comorbidities.[27] Both conditions are associated with T-lymphocyte mediated adaptive immune events and mechanisms involving innate immunity. Reduced numbers and activity of T-regulatory cells and the resulting hyperactivity of Th1/Th17 subsets are encountered in both psoriasis and atherosclerosis, while common innate immune mechanisms include lesional complement activation and toll-like receptor-mediated events leading to cytokine-driven inflammation.[28,29] The term 'psoriatic march' has been used to describe this process, which proceeds in a stepwise manner, beginning with genetic and possibly environmental factors that initiate disease-specific immunologic pathways leading to psoriasis and subsequent comorbidities as a consequence of chronic inflammation. In this model, systemic inflammation associated with psoriasis enhances insulin resistance, causing

Table 1 Severe psoriasis and cardiovascular mortality, myocardial infarction and stroke.

Outcome	Patients, n	HR or RR (95% CI)	Confounders controlled
Cardiovascular mortality			
Abuabara, 2010[14]	Severe psoriasis: 3603 Controls: 14 330	HR 1.57 (1.26–1.96)	Age and gender
Ahlehoff, 2011[15]	Severe psoriasis: 2793 Controls: 4 478 926	RR 1.65 (1.33–2.05)	Age, gender, comorbidities, medication and socioeconomic status
Myocardial infarction			
Gelfand, 2006[16]	Severe psoriasis: 3837 Controls: 556 995	HR 7.08 (3.06–16.36)	Age, gender, hypertension, diabetes, cholesterol, smoking, prior myocardial infarction and body mass index
Mehta, 2011[18]	Severe psoriasis: 3603 Controls: 14 330	HR 1.53 (1.26–1.85)	Age, gender, hypertension, diabetes, cholesterol and smoking
Ahlehoff, 2012[19]	Severe psoriasis: 2793 Controls: 4 478 926	RR 1.45 (1.10–1.90)	Age, gender and medical comorbidities (individual comorbidities not reported)
Stroke			
Gelfand, 2009[20]	Severe psoriasis: 3603 Controls: 14 330	HR 1.43 (1.10–1.87)	Age, gender, hypertension, diabetes, cholesterol, smoking and neurovascular disease
Ahlehoff, 2012[19]	Severe psoriasis: 2793 Controls: 4 478 926	RR 1.65 (1.33–2.05)	Age, gender, social demographics and medical comorbidities (individual comorbidities not reported)

CI: confidence interval; HR: hazard ratio; RR: relative risk.

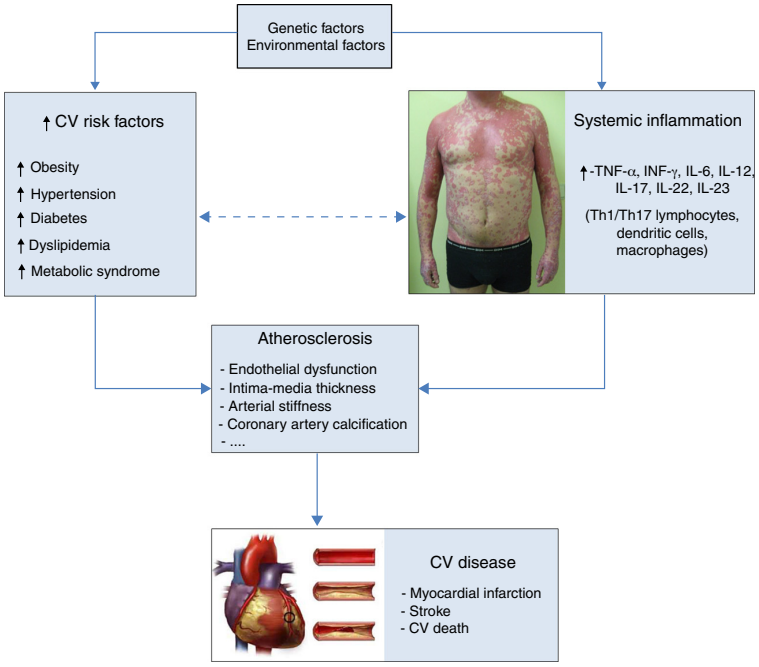

Figure 1 Diagram of the relationships between psoriasis, cardiovascular risk factors, atherosclerosis and cardiovascular disease. CV: cardiovascular.

endothelial dysfunction, atherosclerosis and possible coronary events.[30] Another important factor implicated in the accelerated atherosclerosis observed in psoriasis is the atherogenic side-effects of several systemic agents used to treat psoriasis, such as retinoid-induced dyslipidemia and cyclosporine-induced hypertension.

However, treatment aimed at reducing the severity of the skin disease would also reduce the inflammatory burden. The use of methotrexate and TNF-α inhibitors has been reported to reduce the risk of cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis.[31] In psoriasis, the data are more limited. Improvement in cardiovascular risk biomarkers (high-sensitivity C-reactive protein, vascular endothelial growth factor and the adipokines resistin and adiponectin) has been documented in patients with severe psoriasis responding to continuous systemic therapy, showing that patients' metabolic state improved with inflammatory control.[32] Preliminary evidence suggests that TNF-α inhibitors may improve endothelial function in psoriasis populations and epidemiologic studies show that they may also reduce the risk of adverse cardiovascular events.[33,34]

Despite increasing evidence of the association between psoriasis and cardiovascular disease and the importance of identifying and modifying psoriasis-associated cardiometabolic comorbidities in order to decrease cardiovascular events and mortality, it appears that this has not been fully implemented in clinical practice. A high prevalence of underdiagnosis and undertreatment of cardiovascular risk factors was recently documented in a large cohort of patients (n=2899) with moderate to severe psoriasis enrolled in a phase III clinical trial of ustekinumab; even when these cardiovascular risk factors had been diagnosed there was a high rate of failure to achieve treatment goals in accordance with published guidelines.[35] Additionally, although in 2008 the National Psoriasis Foundation and the American Journal of Cardiology released guidelines for screening and treatment of cardiovascular risk factors in patients with psoriasis, Parsi et al., assessing cardiovascular risk factor screening practice in patients with psoriasis and awareness of primary care physicians and cardiologists of worse cardiovascular outcomes in these patients, found that less than half of these physicians screened patients with psoriasis for cardiovascular risk factors in accordance with the guidelines or were aware of the higher rate of major adverse cardiovascular events in patients with psoriasis compared with the general population, although cardiologists were significantly more likely to screen psoriasis patients for dyslipidemia and were more likely to be aware of their increased cardiovascular risk. Increased experience caring for patients with psoriasis was associated with better adherence to screening guidelines.[36] Increasing the volume of publications in internal medicine and cardiology journals highlighting the association between psoriasis and cardiovascular disease could be a way to improve awareness in the non-dermatology community.

To summarize, the risk of cardiovascular morbidity and mortality is higher in patients with psoriasis than in the general population. Unlike other inflammatory diseases, psoriasis is readily apparent to physicians, both dermatologists and non-dermatologists, which should facilitate prompt evaluation for cardiovascular risk factors and cardiovascular disease.

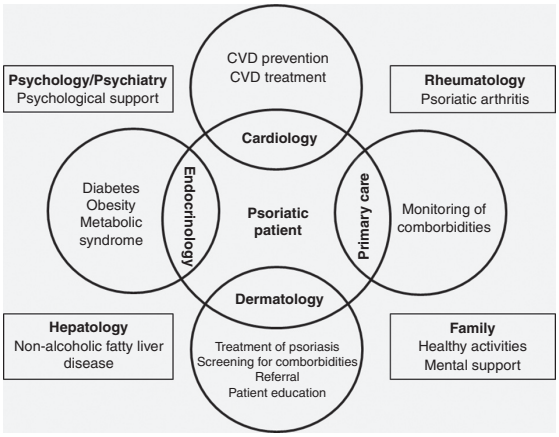

Figure 2 Multidisciplinary approach to the patient with severe psoriasis. CVD: cardiovascular disease.

A multidisciplinary approach should be adopted in the care of patients with psoriasis, particularly in severe cases with multiple comorbidities or cardiovascular disease. Dermatologists are in an important, sentinel-like position, able to detect and respond to early indications of cardiovascular risk factors and comorbidities in psoriasis patients. They should be able to recognize these risk factors, advise and educate patients, and whenever necessary refer them to cardiologists for appropriate treatment. At the same time, cardiologists and other physicians should be aware of this association and the beneficial effect of treating psoriasis on cardiovascular outcomes, and when appropriate refer patients to a dermatologist (Figure 2).

All psoriasis patients should be encouraged to correct their modifiable cardiovascular risk factors, particularly obesity and smoking, and to adopt healthy lifestyle behaviors such as regular exercise. Patients with moderate to severe psoriasis patients, even if otherwise healthy, should be recognized as being at moderately increased risk of cardiovascular disease, and should probably be managed as patients at intermediate risk of cardiovascular disease.

Efforts are needed to develop appropriate treatment strategies and referral networks to ensure appropriate management of these comorbidities, which will likely lead to improvements in patient outcomes.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Importância do Estudo da Influência Genética na associação Psoríase/Doença Cardiovascular

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SHORT COMMUNICATION

Genetic Markers for Cardiovascular Disease in Psoriasis: The Missing Piece

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Abstract Psoriasis is a common, chronic inflammatory disease associated with serious comorbidities. Severe psoriasis has been associated with increase cardiovascular mortality, due to a higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidemia and obesity, and premature atherosclerosis, as a consequence of its systemic inflammation. It is likely that there are genetic links between psoriasis, its comorbidities and cardiovascular disease. Although there are some studies performed in rheumatoid arthritis reporting some gene polymorphisms that may be associated with cardiovascular diseases and comorbidities these studies are lacking in psoriasis. Recognizing genetic markers that could predict which patients are at risk of developing psoriasis-linked cardiovascular comorbidities would facilitate screening strategies and permit an earlier management of cardiovascular risk factors, with important clinical implications.

Psoriasis is a chronic, immune-mediated inflammatory disease affecting 2 % of the global population [1]. In the majority of cases skin manifestations negatively impact on patient's quality of life, however there is mounting evidence that psoriasis is more than a skin disease and it is now widely believed that psoriasis is a systemic inflammatory process, associated with several cardiovascular comorbidities [2].

Diseases that occur concurrently (namely comorbidities) are often thought to be related to common pathogenic mechanisms, shared genetic risk variants, shared environmental triggers or a combination of these factors. Thus, it is likely that there are genetic links between psoriasis and its comorbidities.

Psoriasis has been associated with an increased risk of cardiovascular disease, such as myocardial infarction and stroke [3, 4]. Due to this higher incidence of cardiovascular disease, life expectancy in severe psoriasis is reduced up to 5 years [5]. Moreover, it appears that the age of mortality is linked to age of psoriasis onset, with a longevity decrease as much as 20 years in patients whose psoriasis begins before 25 years [6].

This higher cardiovascular risk may be explained in part by an increased prevalence of classical coronary risk factors, including hypertension, hypercholesterolemia, diabetes mellitus and obesity [7]. On the other hand, some studies have suggested that psoriasis could be an independent risk for cardiovascular disease, as this risk remained after adjustment for the traditional risk factors [8].

Atherosclerosis is driven by inflammation in all pathogenic phases, from initiation of fatty streak to final culmination in acute coronary syndromes, and the inflammatory pathways characterizing psoriasis seem to be involved in the pathogenesis of atherosclerosis, as suggested by the accelerated atherosclerosis observed in psoriasis patients, mainly in the more severe and long-lasting cases [9, 10].

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Psoriasis, atherosclerosis and cardiovascular comorbidities share some pathological features including endothelial dysfunction, alteration in angiogenesis, and some inflammatory pathways including macrophages, dendritic cells, T cells-mediated inflammation and their key-cytokines (TNF-α, INF-γ, IL-1, IL-6, IL-8, IL-12, IL-17, IL-20, IL-23) [10, 11].

Moreover, psoriasis and its associated cardiovascular comorbidities not only affect morbidity and mortality but also healthcare costs [12]. For this reason, identifying patients who present a higher risk of developing these cardiovascular comorbidities is of upmost importance.

Genetic biomarkers are being more commonly used in laboratory medicine to predict the onset of disease or disease recurrence, to individualize treatment, and to assess response to treatment.

Recognizing genetic markers that could predict which patients are at risk of developing psoriasis-linked cardiovascular comorbidities would permit an earlier management, with important clinical implications. Genes encoding pro-inflammatory cytokines, for instance, are candidates for predisposing to cardiovascular disease in psoriasis.

Many pro-inflammatory cytokines, adipokines or pro-angiogenic factors, have been implicated in the pathogenesis of psoriasis and atherosclerosis such as, TNF-α, IL-6, or vascular endothelial growth factor A, while other mediators including endothelin-1, leptin, and resistin have been implicated in the pathogenesis of psoriasis and psoriasis-linked comorbidities, as hypertension, dyslipidemia and obesity [11, 13–16].

The synthesis of these cytokines is tightly regulated at the gene transcription level and partly due by cytokine induction. For instance, approximately 60 % of TNF-α expression may be genetically determined because of specific single-nucleotide polymorphisms (SNP), which are able to increase TNF-α gene expression as shown by its spontaneously enhanced or stimulated production, both in vitro and in vivo [17, 18].

In studies performed in rheumatoid arthritis, it has been reported that some gene polymorphisms, for example, on TNF-α, IL-6, endothelin-1, and ApoE genes may be associated with cardiovascular disease, subclinical atherosclerosis, hypertension or dyslipidemia, reinforcing the potential implication of a genetic component in the development of cardiovascular disease in patients with rheumatoid arthritis [19–22].

However, this kind of studies are lacking in psoriasis. Evaluation of SNPs of cytokine genes, implicated in the pathogeneses of psoriasis, atherosclerosis and cardiovascular comorbidities may be important to elucidate whether particular subsets of psoriasis patients carry a higher risk for the development of cardiovascular and metabolic comorbidities.

Abdel Hay et al. [23] showed that LEP G-2548A polymorphism could be a predictor for higher plasma leptin (as a marker for cardiovascular comorbidity) and for psoriasis, but the authors did not analyse its association with an increased risk of cardiovascular disease or with subclinical atherosclerosis, using surrogate markers of atherosclerosis as endothelial dysfunction or increased carotid artery intima-media wall thickness.

A meta-analysis, conducted by Tian et al. [24], using microarray data from 5 studies consisting in 386 paired-samples from 193 patients, produced a list of differentially expressed genes (DEGs) between lesional and non-lesional skin of psoriasis patients, that are candidate genes for further investigation of psoriasis pathology and biomarker selection, representing a robust reference psoriasis transcriptone, that was termed MAD-5 transcriptone (Meta-Analysis Derived transcriptone). In this study it was included patients with “mild to severe” diseases, while in MAD-3 transcriptione, samples were obtained only from patients with “moderate to severe psoriasis”. Analysis of the list of DEGs in Ingenuity Pathway Analysis (software used to examine data in the context of known biological response and regulatory networks, supported by a published reference) indicated that pathways of great importance such as *Atherosclerosis Signalling* and *Fatty Acid Metabolism* were significantly over-represented in the DEGs list, along with several genes involved in *Cardiovascular Development and Function network* and *Lipid Metabolism*, highlighting the genetic relationship between psoriasis and cardiovascular disease. Moreover it appears that some factors that influence cardiovascular risk may be produced locally in psoriasis skin lesions and become systemically available to increase risk of cardiovascular pathology.

Recently, Lu et al. [25] using the genome-wide association studies (GWAS) catalogue, selected 363 SNPs that showed significant association with coronary artery disease (CAD), hypertension, body mass index, hyperlipidemia and type 2 diabetes and evaluated them for association with psoriasis in four psoriasis GWAS cohorts including 1368, 725, 211 and 2178 psoriasis cases and 1348, 438, 502 and 5175 controls [26, 27]. The authors showed that patients with psoriasis were enriched for certain common genetic variants that predispose to an increased risk for dyslipidemia, hypertension, and increased CAD risk itself. They found SNPs with evidence of shared genetic risk between psoriasis, cardiovascular, and metabolic diseases, as some alleles associated with increased risk for dyslipidemia, increased blood pressure levels, and increased risk for CAD were associated with increased risk for psoriasis. Some SNPs were located in the HLA gene region, which is a known psoriasis susceptibility locus and others were non-HLA SNPs, in FUT2 (encodes an alpha-1,2) fucosyltransferase that determines the secretor status of blood group antigens on epithelial cells), in UBE2L3 (encodes an ubiquitin-conjugating enzyme involved in cell proliferation and

immune function) and near or in SH2B3 (encodes a protein with pleiotropic signaling roles in regulating lymphocyte differentiation, induction of VCAM-1 and E-selectin on endothelial cells by TNF-α and thrombus formation).

Although, these genetic association studies are very important to identify genes and pathways for further investigation, it is also imperative to analyse its association with a higher risk of cardiovascular disease or subclinical atherosclerosis in psoriasis cohorts of patients.

Identifying this kind of genetic markers in psoriasis could be a useful prognostic indicator and facilitate screening strategies that would help clinicians in finding predictors of cardiovascular disease, leading to early, aggressive risk factors management including patient education to adopt healthy life-style behaviours, such as, smoking cessation, weight control and exercise.

Well conducted studies, with a robust number of severe psoriasis patients, analysing whether certain polymorphisms are associated with increased cardiovascular disease, cardiovascular risk factors (hypertension or dyslipidemia) or increased risk of subclinical atherosclerosis manifested by the presence of endothelial dysfunction, increased carotid artery intima-media wall thickness or even coronary artery calcification are needed.

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Actividade Física em Doentes com Psoríase Grave

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ORIGINAL RESEARCH ARTICLE

Levels of Physical Activity in Patients with Severe Psoriasis: A Cross-Sectional Questionnaire Study

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Abstract
Background Psoriasis is a chronic inflammatory disease associated with increased cardiovascular mortality, secondary to the increased prevalence of cardiovascular risk factors and premature atherosclerosis. Physical activity is a vital component in prevention and management of cardiovascular disease. Few studies have examined the level of physical activity in psoriasis patients, using validated questionnaires or other objective assessment tools.
Objective The aim of this study was to analyze and compare physical activity undertaken by patients with severe psoriasis and healthy controls, using the International Physical Activity Questionnaire—Short Form (IPAQ-S), a validated instrument for assessing physical activity.
Methods Ninety patients with severe plaque-type psoriasis and 160 healthy subjects were enrolled in the present study. Physical activity was evaluated using IPAQ-S.
Results Psoriasis patients had reduced levels of physical activity compared with non-psoriasis patients, regardless of sex or whether the variable was continuous or categorical. The odds ratio for low-level physical activity for psoriasis patients, compared with controls, was 3.42 (95 % CI 1.47–7.91), indicating that this severe psoriasis population did not undertake recommended levels of physical activity.
Conclusions Psoriasis patients exhibit decreased levels of physical activity, possibly for both psychological and physiological reasons. The lack of physical activity may contribute to the increased risk of cardiovascular disease in psoriasis patients, in addition to the intrinsic risks related to systemic inflammation and psoriasis-linked comorbidities. Regular physical activity should be encouraged in all psoriasis patients because of its beneficial effects on systemic inflammation and cardiometabolic comorbidities associated with psoriasis.

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1 Introduction

Psoriasis is a chronic, systemic, inflammatory skin disease, which affects 1–3 % of the general population [1]. Psoriasis has been associated with increased cardiovascular mortality, because of a higher prevalence of traditional cardiovascular risk factors (such as hypertension, dyslipidemia, diabetes, obesity, and tobacco use) and premature atherosclerosis, probably as a consequence of systemic inflammation [2–7]. Currently, it is well accepted that all

psoriasis patients should be encouraged to correct their modifiable cardiovascular risk factors, particularly obesity and smoking, and to adopt healthy lifestyle behaviors such as regular physical activity [8]. It is well known that physical activity is vital for the prevention and management of cardiovascular disease, and it has beneficial effects on obesity, diabetes, metabolic syndrome, and other cardiovascular risk factors [9, 10].

Few studies have examined the physical activity of psoriasis patients, and even fewer have used validated questionnaires or objective tools such as accelerometers in their analyses. Instead, in most studies on the physical activity of psoriasis patients, physical activity was analyzed as a secondary objective rather than as a primary study objective, and control groups were lacking, assessment of physical activity was based on a limited number of questions, and study definitions were inconsistent [11].

Despite these shortcomings, previous studies have suggested that physical activity was decreased in psoriasis patients and could be related to the incidence, prevalence, and severity of psoriasis. By contrast, other studies have shown no significant difference in mean physical activity between psoriasis and non-psoriasis patients [12, 13]. A recent study of 30 patients with mild to moderate psoriasis showed that daily physical activity, measured with an accelerometer, was greater in the psoriasis group than in the control group [14].

The aim of this study was to analyze and compare physical activity in patients with severe psoriasis and healthy controls, using a validated instrument to assess physical activity.

2 Methods

Consecutive adult patients with severe plaque-type psoriasis (defined as >10 % of the body surface area [BSA] covered by lesions and/or disease requiring systemic therapy or phototherapy) managed at our Psoriasis Center were enrolled in this cross-sectional study. The control group consisted of relatively healthy patients referred to the dermatology outpatient clinic for management of benign conditions such as nevi, benign skin tumors, or skin infections such as tinea or warts. All recruited patients were more than 18 years old.

Patients were excluded if any of the following were present: psoriatic arthritis (previous/current signs/symptoms indicative of joint involvement); cardiovascular disease, including coronary heart disease (a history of myocardial infarction, angina, angioplasty, or coronary artery bypass grafting), cerebrovascular disease (a history of stroke or transient ischemic attack), or peripheral vascular disease; systemic inflammatory disease (such as lupus erythematous, rheumatoid arthritis, or spondyloarthropathies); or conditions that could impair normal physical activity, such as neurological disease or amputations.

The following patient data were recorded: age, sex, height, weight, presence of cardiovascular risk factors (a previous medical diagnosis or current treatment for hypertension, diabetes, dyslipidemia, tobacco use, and a family history of cardiovascular disease), and current medications. Psoriasis characteristics, including family history, disease duration, current and previous treatments, and severity (as assessed by the Dermatology Life Quality Index [DLQI] questionnaire and BSA covered by lesions, assessed by the same dermatologist, T.T.) were also recorded.

Physical activity was evaluated using a validated, self-report questionnaire known as the International Physical Activity Questionnaire (IPAQ). IPAQ is an instrument designed to assess levels of physical activity, and short and long forms of the questionnaire have been developed on the basis of self-report population surveys. In the present study, the IPAQ Short Form (IPAQ-S) was selected to reduce the burden on participants. IPAQ-S has been developed for adults (15–69 years of age) and tested in this population, and the instrument has been validated in different languages, including Portuguese [15]. IPAQ-S asks participants to report activities that have been performed for at least 10 min in the past 7 days. The amount of physical activity is indicated by the time spent in physical activity during leisure-, work-, domestic- and transport-related activities at three different levels of intensity, which are categorized as "walking", "moderate", and "vigorous" activities. Examples of activities that represent each intensity are provided. Using the instrument's scoring protocol, total weekly physical activity is estimated by weighting time spent in each activity intensity, with its estimated metabolic equivalent (MET) energy expenditure. MET-minutes (MET-min) are calculated by multiplying the MET score of an activity by the minutes for which it is performed, and are equivalent to kilocalories for a 60 kg person. IPAQ-S was found to have fair to moderate agreement with accelerometer-measured physical activity (pooled $r = 0.30$) [15]. IPAQ-S also allows physical activity to be measured as a categorical variable, with the categories defined as "low", "moderate", or "high" levels of physical activity [16]. The definitions for low, moderate, and high levels of physical activity are described in Table 1. Finally, physical activity was separated into either "low-level" or "non-low-level" physical activity, to understand the influence of non-compliance with the recommended physical activity, considering the recent update of the 1995 recommendations on the physical activity needed to improve and maintain health, by the Committee on Exercise and Cardiac Rehabilitation of the American Heart Association: healthy

Table 1 Definitions of low, moderate, and high levels of physical activity [14]

	Definition
Low level	The lowest level of physical activity; it includes the individuals who do not meet criteria for moderate or high physical activity level
Moderate level	Half an hour of at least moderate-intensity physical activity on most days; it includes individuals who meet at least one of the following criteria:
	(a) 3 or more days of vigorous-intensity activity of at least 20 min per day;
	(b) 5 or more days of moderate-intensity activity and/or walking of at least 30 min per day;
	(c) 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum total physical activity of at least 600 MET-minutes/week
High level	At least 1 hour per day, or more, of at least moderate-intensity activity above the basal level of physical activity—basal activity may be considered to be equivalent to approximately 5,000 steps per day, i.e. those who move at least 12,500 steps per day or the equivalent in moderate and vigorous activities; it includes individuals who meet one of the following criteria:
	(a) vigorous-intensity activity on at least 3 days, achieving a minimum total physical activity of at least 1,500 MET-minutes/week;
	(b) 7 days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum total physical activity of at least 3,000 MET-minutes/week

MET metabolic equivalent

adults aged between 18 and 65 years should have moderate-intensity aerobic physical activity for a minimum of 30 min on 5 days each week or vigorous-intensity aerobic physical activity for a minimum of 20 min on 3 days each week—grade of evidence IA [17].

2.1 Statistical Analysis

Continuous variables were expressed as either means ± SDs or medians and interquartile ranges. Categorical variables were expressed as percentages. Variable distribution was tested for normality, using the Kolmogorov–Smirnov test. Patients and controls were compared using the Student's *t* test and the Mann–Whitney *U* test for normally and non-normally distributed continuous variables, respectively. The χ^2 test was used for categorical variables. The odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) were calculated.

The association between disease status (psoriasis patients and controls) and outcome variables was assessed using multivariable logistic and linear regression models, for categorical and continuous variables, respectively, with adjustment for confounders of age and sex.

Pearson's or Spearman's rank correlation coefficients were used to assess the bivariate relationships between continuous and categorical variables and total MET-min among psoriasis patients. The independent association was examined by multivariate linear regression with adjustment covariates of age.

The level of statistical significance was set at $\alpha = 0.05$.

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) Version 21 (SPSS, Chicago, IL, USA).

3 Results

A total of 90 patients with severe psoriasis and 160 healthy subjects were studied. The two groups were similar in terms of sex and age (Table 2). Psoriasis patients had a mean disease duration of 22.1 ± 11.5 years; 39 % had a family history of psoriasis; and their mean BSA covered by lesions and DLQI score were 11.1 ± 7.4 % (54.8 % with BSA > 10 % coverage) and 7.5 ± 6.5 (43.8 % with a DLQI score > 10), respectively. Most patients (83.3 %) were receiving or had previously received systemic therapy or phototherapy.

With respect to cardiovascular risk factors, patients with psoriasis were more likely than controls to have hypertension, diabetes, dyslipidemia, obesity, and an increased body mass index (BMI). No significant statistical differences were observed for a family history of cardiovascular disease and tobacco use. Patients with psoriasis had an increased likelihood (adjusted for age and sex) of having hypertension (OR 2.50, 95 % CI 1.29–4.88), diabetes (OR 4.19, 95 % CI 1.53–11.44), dyslipidemia (OR 1.91, 95 % CI 1.04–3.53), and obesity (OR 2.42, 95 % CI 1.30–4.51) (Table 2).

Analysis of physical activity revealed that the mean total MET-min of psoriasis patients was significantly decreased compared with that of controls ($p = 0.001$). Levels of physical activity of psoriasis patients in each category of intensity (walking, moderate, and vigorous) was less than that of controls, with statistical significance for walking ($p = 0.024$) and moderate intensity ($p = 0.008$), and an underlying trend toward decreased physical activity of vigorous intensity in psoriasis patients ($p = 0.059$). Adjusting for age and sex, the total MET-min and the MET-min in moderate intensity remained statistically significant ($p = 0.002$ and 0.011, respectively), while trends

Table 2 Characteristics of the study subjects

	Psoriasis patients ($n = 90$)	Controls ($n = 160$)	p value#	Adjusted p value*	OR (95 % CI)*
Age [years]	47.7 ± 10.9	46.8 ± 12.2	0.538		
Sex, male [%]	61.1	56.9	0.514$^{\pm}$		
Height [m]	1.68 ± 0.10	1.68 ± 0.08	0.982	0.757	
Weight [kg]	80.8 ± 17.4	72.8 ± 13.2	**<0.001**	**<0.001**	
BMI [kg/m^2]	28.6 ± 5.4	25.8 ± 3.9	**<0.001**	**<0.001**	
BMI categories [%]					
Normal weight	21.1	41.3			
Overweight	46.7	41.9	**0.001**$^{\pm}$		
Obese	32.2	16.9			
Cardiovascular risk factors [%]					
Hypertension	36.7	22.3	**0.018**$^{\pm}$		**2.50 (1.29–4.88)**
Diabetes	15.6	5.0	**0.007**$^{\pm}$		**4.19 (1.53–11.44)**
Dyslipidemia	40.0	27.3	**0.045**$^{\pm}$		**1.91 (1.04–3.53)**
Obesity	32.2	16.9	**0.005**$^{\pm}$		**2.42 (1.30–4.51)**
Tobacco use	32.2	26.6	0.361$^{\pm}$		1.35 (0.74–2.47)
Family history of CVD	5.6	10.8	0.170$^{\pm}$		0.49 (0.17–1.43)
Physical activity assessment [MET-minutes]					
Walking intensity	792 (198–1,675)	1,188 (462–2,376)	**0.024**$^{+}$	0.062	
Male	1,407.1 ± 1,333.9	1,371.3 ± 1,260.5	0.871	0.801	
Female	781.2 ± 863.0	1,609.1 ± 1,307.3	**0.001**	**0.001**	
Moderate intensity	960 (0–1,800)	1,440 (480–2,880)	**0.008**$^{+}$	**0.011**	
Male	480 (0–1,440)	1,080 (240–2,160)	**0.010**$^{+}$	**0.016**	
Female	1,841.1 ± 1,723.5	2,213.7 ± 1,443.5	0.247	0.241	
Vigorous intensity	0 (0–1,260)	480 (0–1,440)	0.059^{+}	0.066	
Male	0 (0–1,440)	480 (0–1,920)	0.296^{+}	0.393	
Female	0 (0–720)	0 (0–1,440)	0.101^{+}	0.070	
Total	3,341.5 ± 3,096.8	4,688.7 ± 3,186.1	**0.001**	**0.002**	
Male	3,413.0 ± 3,104.2	4,305.7 ± 3,354.4	**0.003**	**0.002**	
Female	3,229.2 ± 3,126.8	5,193.9 ± 2,896.3	**0.002**	**0.002**	
Low-level	18.9 %	6.3 %			
Moderate-level	32.2 %	31.3 %	**0.006**$^{\pm}$		
High-level	48.9 %	62.4 %			
Non-low-level	81.1 %	93.7 %			
Low-level	18.9 %	6.3 %	**0.002**$^{\pm}$		**3.42 (1.47–7.91)**

Results are expressed as percentages, medians (interquartile ranges), or means ±standard deviations, as appropriate

Statistically significant p values are labeled with bold text

BMI body mass index, *CI* confidence interval, *CVD* cardiovascular disease, *MET* metabolic equivalent, *OR* odds ratio

Derived using a Student's t test, except where $^{+}$ denotes use of a Mann–Whitney U test and $^{\pm}$ denotes use of a χ^2 test

* Adjusted for age and sex or only age when analyzing physical activity separately by sex

toward decreased MET-min for walking and vigorous intensity were observed in psoriasis patients ($p = 0.062$ and 0.066, respectively) (Table 2).

If the findings were analyzed separately by sex, both male and female psoriasis patients had lower MET minute values than their healthy counterparts. After adjustment for age, the total MET-min and walking MET-min values of female psoriasis patients were significantly decreased, compared with those of female controls ($p = 0.002$ and $p = 0.001$, respectively). In the male group, the total MET-min and moderate-intensity MET-min values were significantly decreased in psoriasis patients compared with controls ($p = 0.002$ and $p = 0.016$, respectively) (Table 2).

Table 3 Impact of physical activity levels on cardiovascular risk factors in psoriasis

	Low-level physical activity [%]	Non-low-level physical activity [%]	*p* value[+]	OR (95 % CI)[a]
Hypertension	47.1	34.2	0.324	1.81 (0.52–6.23)
Diabetes	29.4	12.3	0.130	3.42 (0.88–13.28)
Dyslipidemia	52.9	37.0	0.227	1.87 (0.57–6.14)
Obesity	58.8	26.0	**0.009**	**4.68 (1.47–14.85)**
Tobacco use	23.5	34.2	0.394	0.60 (0.18–2.08)

Statistically significant *p* values are labeled with bold text

CI confidence interval, *OR* odds ratio

[+] χ^2 test

[a] Multivariable logistic regression was used to adjust for age and sex

Categorizing the level of physical activity as low, moderate, or high, there was a statistically significant difference between the psoriasis and control groups ($p = 0.006$). If the level of physical activity was defined as either "low" or "non-low", the sex- and age-adjusted OR for a low level of physical activity among psoriasis patients, versus controls, was 3.42 (95 % CI 1.47–7.91) (Table 2).

In patients with psoriasis, the total MET-min was negatively correlated with weight and BMI ($p = 0.002$ and $p = 0.013$, respectively), although statistical significance was not reached after adjustment for age and sex. No association was observed between total MET-min and psoriasis severity as assessed by BSA coverage ($p = 0.160$) and DLQI score ($p = 0.410$).

Psoriasis patients with "low-level" physical activity (not complying with the recommendations of the American Heart Association) had sex- and age-adjusted OR for obesity of 4.68 (95 % CI 1.47–14.85), compared with psoriasis patients who performed "non-low-level" physical activity, while no significantly higher risk of the other cardiovascular risk factors was observed (Table 3).

4 Discussion

This study showed that psoriasis patients have reduced levels of physical activity, compared with non-psoriasis patients, using a validated instrument, the IPAQ-S.

This decrease in physical activity was observed in both sexes and regardless of whether physical activity was defined as a continuous or categorical variable. The OR for low-level physical activity among psoriasis patients, versus controls, was 3.42 (95 % CI 1.47–7.91), clearly indicating that this severe psoriasis population did not meet the recommendations for healthy physical activity behavior.

In the psoriasis group, the patients who did not meet the recommended levels of physical activity were at greater risk of being obese (OR 4.68, 95 % CI 1.47–14.85) than those who met the recommendations. This finding is particularly important because obesity is a relevant comorbidity in psoriasis.

Consistent with other studies [2–5], the present study demonstrated that patients with severe psoriasis had increased risks of hypertension, diabetes, dyslipidemia, and obesity.

The diminished physical activity of psoriasis patients may be related to psychological barriers. The stigma of psoriasis and social avoidance of these patients might discourage physical activity. In a study of 104 psoriasis patients, most patients showed social avoidance, including avoidance of sports (40 %), collective showers (64 %), wearing sport clothes (64 %), and leaving their home (11.5 %) [18].

Interestingly, in our study, decreased physical activity was not associated with psoriasis severity, assessed using BSA coverage and DLQI scores, even though the two DLQI questions related to sport and leisure activities. In these patients, at least, greater BSA coverage or a greater impact of the disease on patients' quality of life were not associated with decreased physical activities. However, it is currently accepted that psoriasis may present significant cumulative life course impairment, because of the substantial physical, psychological, social and economic burden, which may result in failure to achieve "full life potential" in some patients, as psoriasis influences major life-changing decisions and alters the course of patients' lives, with potentially permanent consequences [19]. Thus, it is possible that, even in lower-severity phases (for example, due to treatment), the previous impact of the disease influences the willingness to do physical exercise.

Physiological barriers may also play a role. Psoriatic patients may not tolerate the same exercise intensity in hot or humid conditions as non-psoriatic individuals do, as psoriatic skin is less effective at dissipating heat and may interfere with sweating [20].

Physical activity may be more important in psoriasis than previously thought. It has recently been shown that reduced physical activity is associated with an increased risk of developing psoriasis. Frankel et al. [21] prospectively evaluated the association between physical activity and the incidence of psoriasis in a large cohort of American women, and observed that vigorous physical activity was independently associated with a reduced risk of psoriasis, which remained significant after adjustment for BMI. This may be due to the modulation of the chronic inflammation that predisposes to the development of psoriasis [21]. Moreover, physical activity appears to have anti-inflammatory effects independent of its effect on fat loss. There is evidence that increasing physical activity can reduce the levels of inflammatory molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, interferon (IFN)-γ, and C-reactive protein—some of which are implicated in the link between psoriasis and its cardiometabolic comorbidities and atherosclerosis—and can elevate levels of anti-inflammatory cytokines such as adiponectin [22, 23]. Finally, physical activity is beneficial in the prevention and management of cardiovascular disease and associated cardiovascular risk factors, which are important contributors to morbidity and mortality in psoriasis. Thus, physical activity may have a role in the treatment and prevention of these conditions in psoriasis patients. Physical activity is essential in weight control and has been demonstrated to decrease leptin levels and increase adiponectin levels, along with enhancing weight loss [24]. Several studies have reported an improvement in psoriasis after weight loss, which was possibly due to a decrease in the levels of proinflammatory mediators associated with excessive adiposity [25–27].

Some limitations of the present study warrant mention. First, the cross-sectional method of the study provided a "snapshot" of a group of individuals but did not allow evaluation of causal relationships. Also, it was not possible to analyze the effect of physical activity on different aspects of the disease. Second, although the use of a validated instrument to evaluate physical activity may be regarded as a strength of this study, IPAQ-S is a self-report assessment of physical activity and has been shown to overestimate physical activity, when compared with data measured by an objective method [28]. Thus, the actual physical activity of study subjects may have been even lower than was reported in the present study. Prospective studies using objective tools such as accelerometers or pedometers are needed to evaluate the influence of physical activity on psoriasis severity, response to treatment, and psoriasis comorbidities.

Despite these limitations, the authors believe that the present study is important because it assessed the physical activity of severe psoriasis patients, using a validated instrument in the presence of a considerable control group.

5 Conclusion

This study has demonstrated that patients with severe psoriasis have decreased levels of physical activity compared with non-psoriasis individuals, probably for both psychological and physiological reasons. Psoriasis patients, particularly those with severe disease, have recognized increased risks of cardiovascular disease and cardiometabolic comorbidities. In addition, it appears that physical activity—an important preventive measure and an effective treatment for these cardiovascular conditions—is reduced in psoriasis patients. Thus, besides the intrinsic risks related to systemic inflammation and psoriasis-linked comorbidities, the lack of physical activity may represent an additional risk factor for cardiovascular disease in these patients.

Physical activity may have a dual beneficial effect in psoriasis, affecting its risk and probably its severity, through effects on systemic inflammatory mediators, and having a positive effect on the cardiometabolic comorbidities associated with psoriasis.

All psoriasis patients should be encouraged to correct their modifiable cardiovascular risk factors, such obesity and smoking, and to adopt a healthy lifestyle that includes regular physical activity.

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Impacto da Psoríase no Diagnóstico e Tratamento dos Factores de Risco Cardiovasculares e na Prevenção Primária de Eventos Cardiovasculares

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CONCISE COMMUNICATION

Framingham Risk Score underestimates cardiovascular disease risk in severe psoriatic patients: Implications in cardiovascular risk factors management and primary prevention of cardiovascular disease

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ABSTRACT

Severe psoriasis has been associated with increase cardiovascular mortality, due to a higher prevalence of traditional cardiovascular risk factors and premature atherosclerosis, as a consequence of its systemic inflammation. Recently, it has been estimated that severe psoriasis may confer an increased 6.2% on long-term risk of cardiovascular disease based on Framingham Risk Score, which can have practical implications in the treatment of cardiovascular risk factors and primary prevention of cardiovascular disease, as treatment guidelines account for the risk of cardiovascular disease in treatment goals. The aim of this study was to analyze the influence of the attributable risk of severe psoriasis on long-term risk of cardiovascular disease and its implication on the correct treatment of cardiovascular risk factors and primary prevention of cardiovascular disease on a real-world cohort of patients. One hundred severe psoriasis patients without psoriatic arthritis or previous cardiovascular disease were evaluated and it was found that more than half of the patients were reclassified to a higher cardiovascular risk category with important clinical implications on the correct management of their cardiovascular risk factors and primary prevention of cardiovascular disease, as a considerable proportion of patients with hypertension, hypercholesterolemia and coronary heart disease equivalent risk were not being correctly managed.

Key words: cardiovascular disease, cardiovascular risk factors, Framingham Risk Score, psoriasis, treatment goals.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects approximately 3% of the population.[1] In past years, an increased mortality due to cardiovascular diseases (CVD), such as myocardial infarction and stroke, has been documented in patients with severe psoriasis.[2] For this reason, these patients appear to have a shorter life expectancy, estimated as approximately 5 years.[2]

Psoriatic patients have increased prevalence of traditional cardiovascular risk factors (CVRF) such as diabetes, hypertension, dyslipidemia, tobacco use and obesity.[3] Moreover, psoriasis, mainly if severe, appears to be an independent risk factor for atherosclerotic CVD, as the risk persists even after adjusting for the traditional risk factors, probably due to its systemic inflammation, responsible for the premature atherosclerosis seen in these patients.[4]

Framingham Risk Score (FRS) estimates the long-term risk of CVD analyzing the traditional CVRF, such as age, sex, smoking status, systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and diabetes mellitus, stratifying patients into three risk categories: low (<10%), intermediate (10–20%) and high (>20%).[5] However, this may underestimate this risk in severely psoriatic patients, not accounting for the excess risk attributable to severe disease. Similarly to rheumatoid arthritis (RA), that risk score models should be adapted for RA patients by introducing a 1.5 multiplication factor,[6] Methta *et al.*[7] estimated the attributable risk that severe psoriasis confers on 10-year major adverse cardiac events, which was found to be 6.2%. Moreover, they showed that it could have practical implications in the treatment of CVRF in such patients.[8]

Cardiovascular risk factors treatment guidelines, for hypertension and hypercholesterolemia, account for the risk of CVD

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in treatment goals. For example, the treatment goal for LDL-C is 160 mg/dL for low-risk patients, and 130 and 100 mg/dL for intermediate and high-risk patients, respectively.[9] Likewise, SBP/diastolic blood pressure (DBP) goal is less than 130/80 mmHg for high-risk patients instead of 140/90 mmHg for non-high-risk patients.[10] Moreover, according to National Cholesterol Education Program guidelines, patients with FRS greater than 20% in the absence of atherosclerotic CVD or diabetes are patients with coronary heart disease (CHD) risk equivalent. In such patients, especially in the presence of other CVRF, treatment with aspirin and statins may be considered.[9,11]

As a recent high proportion of underdiagnosis and inadequate treatments of these CVRF in patients with severe psoriasis has been documented,[12] correct screening, monitoring and treatment of CVRF has gained higher importance.

The authors decided to analyze the influence of the attributable risk of severe psoriasis estimated by Methta *et al.*[7] (6.2%) on long-term risk of CVD based on FRS and its implication in the correct treatment of CVRF and primary prevention of cardiovascular disease.

METHODS

One hundred consecutive patients with severe plaque-type psoriasis (Psoriasis Area and Severity Index [PASI] >10 and/or biologic/phototherapy) without psoriatic arthritis (no previous/current signs/symptoms of joint evolvement) or previous CVD (ischemic heart disease, cerebrovascular disease or peripheral arteriopathy) were observed in a dermatology outpatient clinic of a tertiary hospital. For the purpose of this analysis, patients currently under treatment or treated in the previous 4 months with retinoids or cyclosporin were not included due to possible effects on blood pressure and lipid profile.

All patients underwent clinical evaluation, including complete medical history and physical examination and a thorough laboratory evaluation. The following information was systematically recorded: demographic characteristics, psoriatic disease duration, severity and current therapy, medical history of cardiovascular risk factors and therapy. Blood pressure was the mean of three measurements taken at 5-min intervals on the right arm with the patient in a seated position after at least 5 min rest. Blood tests included fasting glucose and insulin, hemoglobin A1c, leptin, high-sensitivity C-reactive protein and fasting serum lipids (total cholesterol, HDL-C, LDL-C, very low-density lipoprotein cholesterol, oxidized LDL-C, triglycerides, lipoprotein[a] and apolipoprotein B). FRS was calculated for each subject using the risk score of Wilson *et al.*[5] Metabolic syndrome was defined by the definition of the National Cholesterol Education Program Adult Treatment Panel (ATP III) guidelines.[13]

RESULTS

The mean age was 48.0 ± 10.3 years (range, 30–70) and 64% were men; 82% had undergone previous systemic/phototherapy/biologic treatment, although at the time of the observation only 23% were under systemic therapy, with most patients (79%) having a PASI of more than 10. Considering the prevalence of CVRF, 49% had hypertension (male 51.6%; female 44.4%), 36% were hypercholesterolemic (male 42.3%; female 25%), 37% of the patients were obese (male 31.2%; female 47.2%), 13% were diabetic (male 12.5%; female 13.9%), 20% were current smokers (male 25%; female 11.1%) and 34% had metabolic syndrome (male 34.7%; female 33.3%). Mean body mass index was 28.79 ± 5.19 (male 28.22 ± 4.38; female 29.80 ± 6.34).

Mean FRS was 8.39% ± 7.07 (male 9.64% ± 6.81; female 6.17% ± 7.05), with 71%, 22% and 7% classified at low, intermediate and high risk, respectively. After considering the estimated attributable risk for severe psoriasis, the mean FRS increased to 14.59% ± 7.07 (male 15.84% ± 6.81; female 12.37% ± 7.05); 57% of the patients were reclassified as higher risk (68.8% of the men and 36.1% of the women), 63.4% of patients at low risk were reclassified as intermediate risk and 54.5% of those at intermediate risk were reclassified as high risk (26%, 55% and 19% at low, intermediate and high risk, respectively) (Tables 1,2).

Interestingly, 65.3% of the patients with hypertension and 63.9% of the patients with hypercholesterolemia were reclassified as higher risk (hypertension, 40.8% to intermediate risk and 24.5% to high risk; hypercholesterolemia, 38.9% to intermediate risk and 25% to high risk). Moreover, this reclassification had important implications in the correct treatment of patients with hypertension and hypercholesterolemia; after the reclassification, 28.6% of the patients considered well treated

Table 1. Demographic and clinical data

	Total, *n* = 100	Men, *n* = 64	Women, *n* = 36
Age, years*	48.0 ± 10.3	48.2 ± 9.8	47.8 ± 11.3
Family history of psoriasis	41%	40.7%	41.7%
Psoriasis duration, years*	20.3 ± 11.3	20.3 ± 10.0	25.9 ± 12.7
Psoriasis severity (at the time of evaluation)			
PASI ≤10	21%	18.8%	25%
PASI >10	79%	81.%	75%
Previous treatment			
Topical only	18%	18.8%	16.7%
Phototherapy	57%	50%	69.4%
Systemic (conventional/biologic)	70%	68.8%	72.2%
Current treatment			
Topical treatment	78%	81.2%	72.2%
Systemic (methotrexate, cyclosporin, acitretin)	0%	0%	0%
Phototherapy	2%	1.6%	2.8
Biologic therapy	20%	17.2%	25%

*Mean ± standard deviation.

for hypertension were not following guideline treatment goal recommendations (SBP/DBP <130/80 mmHg for high-risk patients), while 42.9% of patients being treated for hypercholesterolemia were considered undertreated (treatment goals: 160 mg/dL for low-risk, 130 mg/dL for intermediate-risk and 100 mg/dL for high-risk patients). Additionally, none of the patients who were reclassified as high risk (CHD risk equivalent) was receiving aspirin and 40% were not receiving statins.

DISCUSSION

As recognized by the ATP III, there are emerging risk factors that are not captured in the FRS, contributing to CHD risk to varying degrees. Similar to RA, severe psoriasis is one of them. In fact, it has been reported that assessing cardiovascular disease risk using scores such as FRS in severely psoriatic patients may underestimate the real risk for CVD, as it does not take into account its independent risk, naturally, with important clinical implications in the management of CVRF and CVD prevention in these patients.[7,8]

Considering the estimated attributable risk for severe psoriasis on long-term risk of CVD based on the FRS (6.2%) in a real-world cohort of severely psoriatic patients without psoriatic arthritis, it was observed that a considerable proportion of the patients was reclassified to a higher risk category and that 28% and 42% of the patients considered well treated for hypertension and hypercholesterolemia, respectively, were undertreated if considering their new CVD risk category. Moreover, and of more importance, it had implications in the correct primary prevention of CVD, as a significant proportion of severely psoriatic patients may be at CHD equivalent risk and not being managed as such.

Although the most suitable system of CVD risk estimation for European populations is SCORE (Systematic Coronary Risk Evaluation), developed in 2004 because of concerns that FRS could overestimate the risk of CVD disease in European populations, there is evidence that risk estimates based on Framingham data generalize well to other populations at similar levels of risk both in the USA and Europe.[14] Moreover, most data evaluating the CVD risk in psoriasis patients, including European populations

Table 2. Patients' cardiovascular risk factors and risk evaluation

	Total, *n* = 100	Men, *n* = 64	Women, *n* = 36
Diabetes (%)	13%	12.5%	13.9%
Hypertension (%)	49%	51.6%	44.4%
Hypercholesterolemia (%)	36%	42.3	25%
Hypertriglyceridemia (%)	19%	26.6%	5.6%
Tobacco use (%)	20%	25%	11.1%
Body mass index*	28.79 ± 5.19	28.22 ± 4.38	29.80 ± 6.34
Normal weight	17%	18.8%	13.9%
Overweight	46%	50%	38.9%
Obese	37%	31.2%	47.2%
Waist circumference, cm*	96.37 ± 12.8	96.55 ± 10.91	96.06 ± 15.84
Waist-to-height ratio*	0.580 ± 0.08	0.565 ± 0.068	0.607 ± 0.093
Metabolic syndrome (%)	34%	34.7%	33.3%
Systolic blood pressure, mmHg*	134.0 ± 16.0	135.2 ± 15.5	131.8 ± 16.9
Diastolic blood pressure mmHg*	80.9 ± 8.9	82.1 ± 8.8	78.6 ± 8.9
10-year Framingham Risk Score (LDL-C)*			
Without psoriatic attributable risk	8.39% ± 7.07	9.64% ± 6.81	6.17% ± 7.05
With psoriatic attributable risk	14.59% ± 7.07	15.84% ± 6.81	12.37% ± 7.05
Glucose, mg/dL†	87 (79–100)	93 (81.3–100.8)	81.5 (76.0–93.0)
HgA1c%†	5.4 (5.2–5.6)	5.4 (5.2–5.6)	5.4 (5.2–5.7)
Total cholesterol, mg/dL*	207.4 ± 40.3	204.2 ± 33.6	213.2 ± 50.4
HDL-C, mg/dL*	51.2 ± 13.1	47.1 ± 10.6	58.5 ± 14.0
LDL-C, mg/dL*	130.1 ± 38.8	47.1 ± 10.6	133.9 ± 45.3
VLDL-C, mg/dL†	22.0 (14.3–33.8)	24.5 (17–42.5)	18.5 (13.0–24.8)
Oxidized LDL-C, mg/dL*	184.8 ± 56.8	189.8 ± 53.3	176.0 ± 62.3
Triglycerides, mg/dL†	108.5 (72.5–155.8)	113.5 (84–193.5)	93.5 (65.3–124.8)
Apolipoprotein B, mg/dL*	94.6 ± 24.3	96.1 ± 21.6	91.8 ± 28.6
Lipoprotein(a), mg/dL†	22.5 (5.3–45.5)	21.0 (4.3–43.3)	25.5 (6.0–47.8)
High-sensitivity CRP, mg/dL†	2.4 (2.3–4.8)	1.82 (0.9–4.1)	3.3 (1.1–5.8)
Insulin, μU/mL†	10.4 (10.4–15.5)	11 (7.5–16.3)	9.8 (6.4–14.3)
Leptin, ng/mL†	0.70 (0.70–1.6)	0.51 (0.26–0.73)	1.5 (0.8–2.8)
HOMA >2.5 (excluding diabetic patients)	34.5%	41.1%	22.6%

*Mean ± standard deviation. †Median (interquartile range). CRP, C-reactive protein; HOMA, Homeostasis Model of Assessment; HDL-C, high-density lipoprotein cholesterol; HgA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

used FRS[15] and more importantly the attributable risk of severe psoriasis estimated by Metha *et al.* was calculated using the FRS.

In summary, due to this higher risk attributable to the disease, probably owing to its systemic inflammation, these patients should be more aggressively treated and controlled for their CVRF. Current treatment goals for CVRF, such as hypertension and hypercholesterolemia, may be inappropriate for patients with severe psoriasis and should be reevaluated for such patients, similarly to what has been done for RA patients with the recent European League Against Rheumatism evidence-based recommendations on managing CVD risk in patients with RA and psoriatic arthritis.[6]

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Disfunção Eréctil como marcador precoce de Risco Cardiovascular em Doentes com Psoríase

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Clinical report

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Erectile dysfunction in psoriasis patients

Background: An association between psoriasis and sexual dysfunction has been explored. However, not much is known about the factors behind erectile dysfunction in these patients. *Objectives*: To compare the prevalence and the severity of erectile dysfunction in patients with and without psoriasis and to determine potential associations between erectile dysfunction and psoriasis patients' characteristics. *Materials & Methods*: An observational cross-sectional study was conducted at two tertiary hospital-based Dermatology departments. Consecutive adult men with psoriasis or other skin conditions were recruited. Data were collected using an anonymous, self-completed, designed questionnaire, which included the Dermatology Life Quality Index and the 5-item version of the International Index of Erectile Function. *Results*: A total of 135 psoriasis patients and 201 controls were included. Psoriasis patients had a higher prevalence of erectile dysfunction than controls (61.5% *vs* 43.8%, p = 0.001), and an increased risk of more severe forms of erectile dysfunction. Dermatology Life Quality Index, genital psoriasis and psoriasis duration were not associated with the presence of erectile dysfunction. In multivariate logistic regression, psoriasis and diabetes were found to be independent risk factors for erectile dysfunction with estimated odds ratios of 2.28 (CI 95%, 1.40-3.27) and 3.49 (CI 95%, 1.40-8.66), respectively. *Conclusion*: This study suggests psoriasis as a risk factor for erectile dysfunction. Atherosclerosis is a plausible connecting link, adding up to the already acknowledged effect of psychological factors in these patients. From a clinical standpoint, because erectile dysfunction may precede overt cardiovascular disease, it can be used as a precocious marker of cardiovascular risk in psoriatic men.

Key words: erectile dysfunction, psoriasis

Psoriasis is a chronic, systemic, inflammatory skin disease that affects approximately 2-4% of the population [1]. This condition has a significant negative impact on patients' quality of life, affecting both physical and psychosocial well-being [2]. Psoriasis has been associated with a number of behavioural and systemic comorbidities, including depression, obesity, hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome and cardiovascular disease [3]. Regarding the latter, proatherogenic systemic inflammation is thought to promote premature and subclinical atherosclerosis, ultimately increasing the risk of cerebrovascular and ischemic heart diseases in psoriasis patients [4, 5].

The National Institutes of Health defines erectile dysfunction (ED) as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [6]. In addition to psychological factors, ED usually has a physical etiology. Atherosclerosis is a common cause of ED. In fact, penile atherosclerosis/vascular ED has been considered an expression of systemic endothelial dysfunction and is often a neglected marker of cardiovascular risk [7, 8].

An association between psoriasis and sexual dysfunction has been explored. However, other than the psychological dimension of psoriasis [9-14], not much is known about the factors behind ED in these patients.

The present study aimed to compare the prevalence and the severity of ED in patients with and without psoriasis, and to determine potential associations between ED and psoriasis patients' characteristics.

Patients and methods

An observational cross-sectional study was conducted at two tertiary hospital-based Dermatology departments. Consecutive adult men attending outpatient Dermatology appointments were enrolled. Informed consent was granted beforehand, along with establishing the physical and mental capability to participate in the study. Patients were categorized in two groups according to their clinical diagnosis: the psoriasis and the control groups. The psoriasis group included patients with severe psoriasis (Psoriasis Area Severity Index [PASI]>10 and/or under systemic therapies) without psoriatic arthritis (no previous/current signs/symptoms of joint involvement). The control group consisted of patients with skin conditions other than psoriasis, such as benign skin tumours, superficial skin infections or eczema. Exclusion criteria included, for both groups, the presence of cardiovascular disease, defined as the presence

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of coronary heart disease (myocardial infarction, angina, angioplasty or coronary artery bypass grafting), cerebrovascular accident (stroke or transient ischemic attack) or peripheral vascular disease, of autoimmune or inflammatory systemic diseases, as well as the existence of clinical conditions that could be associated with ED (namely hormonal, testis, and prostate or penis conditions, along with column fracture or surgery).

Data were collected during clinic attendance, using an anonymous, self-completed, designed questionnaire. The following information was systematically recorded for psoriasis patients and control subjects: age, height, weight, known cardiovascular disease (as previously stated), and presence of cardiovascular risk factors (CVRF) (previous medical diagnosis or current treatment for hypertension, diabetes, dyslipidemia and tobacco use). Participants were asked about the presence of any disease that could determine sexual dysfunction, as formerly stated. The use of medical devices or drugs for the treatment of ED was also registered. For patients with psoriasis, information regarding disease duration, involvement of genital skin, and treatment (phototherapy, topical, systemic agents) were recorded.

Both groups answered the Dermatology Life Quality Index (DLQI) and the 5-item version of the International Index of Erectile Function (IIEF-5). The last-mentioned consists of a multidimensional scale for assessment of ED severity that addresses relevant domains of male sexual function, that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. An IIEF-5 score $\leq$21 discloses the presence of ED.

The Ethics Committee of both centres approved the study protocol.

Statistical analysis

Descriptive statistics are presented as a percentage for categorical variables and as a mean with standard deviation or median with interquartile range (IQR) for continuous variables. Variable distribution was tested for normality using the Kolmogorov-Smirnov test. Log transformation was performed for non-normal variables.

Patients and control subjects were compared using Student's *t*-test for continuous variables and the chi-squared test for categorical variables. The association between disease status (psoriasis and controls) and the outcome variables was assessed using multivariable logistic and linear regression models for categorical and continuous variables, respectively, with adjustment for confounders. A multivariate logistic regression model was built with the categorical variable "presence of erectile dysfunction (IIEF-5$\leq$21)" as dependent variable to analyse an independent association between disease psoriasis and ED. A univariate analysis of each variable was first carried out and those that were significant ($p<0.10$) were included in the logistic regression model. Among psoriasis patients, the relationship between the presence of ED and anthropomorphic measures, cardiovascular risk factors and psoriasis characteristics was examined by multivariate logistic regression with adjustment for age as covariate. The level of statistical significance was set at $\alpha = 0.05$.

The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 21 (SPSS, Chicago, IL).

Results

A total of 135 psoriasis patients and 201 controls were studied *(table 1)*. Both groups were similar regarding age. Psoriasis patients had a higher body mass index (BMI) compared to controls ($p = 0.009$), and this difference was statistically significant even after adjustment for age ($p = 0.007$). Concerning the prevalence of CVRF, no difference was found between the two groups.

The mean psoriasis duration was 18.9 $\pm$ 10.2 years. A total of 26.7% of patients had genital psoriasis. The median DLQI was 3 (IQR 1-7). With reference to psoriasis therapy, 89.6% were receiving systemic or phototherapy, including biological therapy in 35.6%.

Association of disease status with ED

Psoriasis patients had a higher prevalence of ED (IIEF-5$\leq$21) than controls (61.5% *vs* 43.8%, $p = 0.001$), with a 2.09-fold higher risk of having ED, independent of age and CVRF (OR 2.09, CI 95%, 1.31-3.35) *(table 1)*.

Moreover, psoriasis patients had more severe ED: IIEF-5 was significantly lower than in control subjects (19.23 ± 5.11 *vs* 20.92 ± 3.72, $p = 0.001$), even after adjustment for age and CVRF ($p<0.001$). When compared to controls, psoriasis patients had a 2.69 and 5.3-fold increased risk of having mild-moderate and moderate-severe ED, respectively *(table 1)*.

A multiple regression model was performed considering the variables with a $p<0.100$ in univariate analysis (age, height, BMI, hypertension, diabetes, dyslipidemia and obesity). ED (IIEF-5$\leq$21) was independently associated with psoriasis ($p = 0.001$), height ($p = 0.002$) and diabetes ($p = 0.007$). Psoriasis was found to be an independent risk factor for ED with an estimated OR of 2.28 (CI 95%, 1.40-3.27). The estimated OR for ED in patients with diabetes was 3.49 (CI 95%, 1.40-8.66) *(table 2)*.

Association of anthropomorphic measures, cardiovascular risk factors and psoriasis characteristics with ED in patients with psoriasis

Within psoriasis patients, age, height, and diabetes were associated with ED ($p<0.05$). There were no differences regarding DLQI between psoriasis patients with and without ED. Genital involvement was higher in those patients without DE, although this difference was not statistically significant. Similarly, psoriasis duration was not associated with the presence of ED *(table 3)*.

Discussion

Few studies have addressed sexual dysfunction in patients with psoriasis. Evidence supports an increase of ED in this subset of patients [9, 10, 14]. Up until recently, the emphasis of these studies was on the psychological aspects of psoriasis and its impact in sexual health [9-14]. Feelings such as anxiety, shame, and depression, especially in the presence of genital lesions, have been associated with sex-

Table 1. Group characteristics according to responses to the questionnaire.

	Psoriasis (n = 135)	Controls (n = 201)	p-value	p-value*
Age, y	47.27 ± 11.36	47.48 ± 15.27	0.886	. . .
Height	1.73 ± 0.08	1.72 ± 0.07	0.105	0.091
Weight	82.59 ± 15.60	77.47 ± 12.30	**0.002**	**0.001**
BMI	27.33 ± 4.15	26.16 ± 3.92	**0.009**	**0.007**
Psoriasis characteristics				
Disease duration, y	18.9 ± 10.2	. . .		
Genital psoriasis	26.7%	. . .		
DLQI	3 (1-7)	. . .		
Psoriasis treatment				
Topical therapy	10.4%	. . .		
Phototherapy	28.1%	. . .		
Conventional systemic therapy	25.9%	. . .		
Biologic therapy	35.6%	. . .		
Cardiovascular risk factors			p-value	OR (95% CI)*
Hypertension	33.3%	27.4%	0.241	1.65 (0.97-2.82)
Diabetes	12.4%	11.4%	0.750	1.35 (0.66-2.76)
Hyperlipidemia	40.0%	33.8%	0.249	1.37 (0.86-2.19)
Obesity	17.8%	14.4%	0.409	1.32 (0.73-2.39)
Tobacco use	28.9%	26.4%	0.611	1.16 (0.71-1.90)
Erectile dysfunction assessment				OR (95% CI)#
With ED (IIEF-5: ≤21)	61.5%	43.8%	**0.001**	**2.09 (1.31-3.35)**
ED severity				
No ED (IIEF-5: 22-25)	38.5%	56.2%		1
Mild (IIEF-5: 17-21)	31.1%	31.8%		0.93 (0.58-1.50)
Mild-moderate (IIEF-5: 12-16)	21.5%	10.0%		**2.96 (1.51-5.82)**
Moderate-severe (IIEF-5: 5-11)	8.9%	2.0%	<**0.001**	**5.30 (1.62-17.37)**
				p-value#
IIEF-5	19.23 ± 5.11	20.92 ± 3.72	**0.001**	<**0.001**

**Adjusted for age. #Ajusted for age and cardiovascular risk factors.BMI, body mass index; DLQI, Dermatology Life Quality Index; ED, erectile dysfunction; IIEF-5, 5-item version of the International Index of Erectile Function; OR, odds ratio; CI, confidence interval.*

Table 2. Univariate and multivariate logistic regression analysis for erectile dysfunction.

	Univariate analysis		Multivariate analyses	
	Unadjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Psoriasis	2.05 (1.31-3.20)	0.002	2.28 (1.40-3.72)	0.001
Age	. . .	<0.001	. . .	0.240
Height	. . .	0.002	. . .	0.002
Weight	. . .	0.488	. . .	. . .
BMI	. . .	0.002	. . .	0.302
Hypertension	2.28 (1.40-3.69)	0.001	1.14 (0.63-2.08)	0.669
Diabetes	5.40 (2.31-12.59)	<0.001	3.49 (1.40-8.66)	0.007
Hyperlipidemia	1.96 (1.25-3.09)	0.004	1.34 (0.80-2.25)	0.272
Obesity	2.03 (1.09-3.76)	0.025	1.44 (0.55-3.79)	0.458
Tobacco use	0.79 (0.49-1.29)	0.350	. . .	. . .

BMI, body mass index; OR, odds ratio; CI, confidence interval.

ual distress [9, 11-13]. However, ED in psoriasis is most likely multifactorial. In fact, a previous study has explored the possible link between atherosclerosis and ED in psoriasis. Whilst this association was not clearly statistically established, the increased prevalence of ED in the psoriasis group was not entirely explained by psychosocial factors, raising the possibility of an atherosclerotic etiology [15].

Table 3. Analysis of erectile dysfunction in patients with psoriasis.

	Without ED (IIEF-5 >21)	With ED (IIEF-5 ≤21)	p-value	p-value*
N (%)	52 (38.5%)	83 (61.5%)	...	...
Age	42.9 ± 10.34	50.0 ± 11.20	**<0.001**	...
Weight	85.2 ± 17.04	80.9 ± 14.48	0.123	0.137
Height	1.77 ± 0.07	1.71 ± 0.08	**<0.001**	**0.004**
BMI	27.2 ± 27.17	27.4 ± 3.89	0.704	0.850
Hypertension	28.8%	36.1%	0.381	0.702
Diabetes	1.9%	19.3%	**0.003**	**0.050**
Hyperlipidemia	36.5%	42.2%	0.516	0.666
Obesity	13.5%	20.5%	0.299	0.525
Tobacco use	38.5%	22.9%	0.052	0.204
Psoriasis duration	18.2 ± 9.4	19.4 ± 10.8	0.522	0.664
DLQI	4.1 ± 4.3	4.6 ± 4.7	0.634	0.812
Genital psoriasis	34.6%	21.7%	0.098	0.600

**Adjusted for age.BMI, body mass index; DLQI, Dermatology Life Quality Index; ED, erectile dysfunction; IIEF-5, 5-item version of the International Index of Erectile Function.*

The current study has further demonstrated an increased prevalence of ED in patients with psoriasis. These patients exhibited two-fold increased odds of having ED and more severe forms of ED when compared to control subjects, independently of age and traditional CVRF. In fact, psoriasis was found to be an independent risk factor for ED. Interestingly, factors such as DLQI, disease duration, and genital disease did not statistically contribute to ED in psoriasis patients. This perhaps suggests that psychological factors were not so relevant in our cohort of patients, supporting the possibility of an association between subclinical atherosclerosis and ED in psoriasis.

Diabetes mellitus was also found to be an independent risk factor to ED, in agreement with current literature [16]. There were not, however, statistically significant differences between the two groups regarding the prevalence of diabetes.

Mounting evidence has emerged indicating that psoriasis is an independent risk factor for the development of cardiovascular disease [17], and atherosclerosis may be the connecting link [4]. Comorbidities, inflammation, and medication are conceivable contributors. The higher prevalence of traditional CVRF, such as obesity, hypertension, diabetes mellitus, hyperlipidemia (often combined as metabolic syndrome), and tobacco use, along with the atherogenic side-effect of some antipsoriatic therapeutics, add up as risk factors for atherosclerotic disease [3, 18]. Moreover, chronic inflammation is presently proposed as a direct cause of subclinical atherosclerosis observed in psoriasis patients with or without joint involvement [4, 5].

ED is nowadays recognized as a precocious indicator of systemic endothelial dysfunction that may precede overt CVD. Androgens, medication, chronic inflammation, and CVRF collectively contribute to atherosclerosis, resulting locally in disorders of penile and coronary circulation. Since penile artery size is smaller than coronary arteries, the reduction of blood flow is observed earlier in erectile tissues than in coronary circulation. From a clinical perspective, because ED may precede CVD, it can be used as an early marker of cardiovascular risk in men [8, 19]. This is also likely valuable for many patients with psoriasis, particularly for those with moderate to severe presentations, with a therapy history that includes atherogenic antipsoriatic drugs, and for those with concomitant traditional CVRF. In this sense, the diagnosis of ED may offer a window of opportunity for intervention before the occurrence of cardiovascular events. As for other subpopulations, psoriasis patients with ED at high risk of CVD should undergo a cardiologic assessment and receive treatment of risk factors.

We acknowledge some limitations to this study. Firstly, as an observational cross-sectional study, causal inference is limited. In addition, some potential participants might have been discouraged to take part in the study due to the subject matter, introducing a selection bias, thus decreasing the true prevalence of ED in both groups. Still, the use of an anonymous self-reported questionnaire has probably precluded for the most part this limitation. As for any self-reported survey we admit some response bias, either intentionally or due to comprehension factors. It would have also been of interest to detail drug history, not only previous systemic antipsoriatics but also antihypertensive medication as an indirect cause of ED. Nevertheless, recent studies have shown a high prevalence of undiagnosed and undertreated hypertension and other CVRF in psoriasis patients when compared and matched to individuals from the general population [20, 21]. Another limitation comprises de non-inclusion of analytic markers of atherosclerosis and inflammation in this study that could help the interpretation of causality between variables. On the other hand, this is the largest study of ED in psoriasis patients enrolling two different tertiary centers specialized in the care of moderate to severe psoriasis. Additionally, both psoriasis and control groups were adjusted for homogeneity of populations, including the exclusion of patients with clinical CVD.

In our opinion, more studies on this subject are needed. It would be interesting not only to include analytic markers, as previously stated, but also imaging studies of the pelvic and coronary circulation. Subanalysis of ED prevalence and severity in patients with and without psoriatic arthropathy is also appealing, based on the greater burden of inflammation in the latter.

In conclusion, the present findings suggest that psoriasis is an independent risk factor for ED. We highlight the potential association between atherosclerosis, ED and psoriasis, and the utility of ED as a precocious marker of CVD. From a clinical standpoint, routine assessment of ED may be useful and patients with ED and a high risk of CVD should undergo comprehensive cardiovascular screening and thorough treatment of risk factors. ■

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Complemento C3 como marcador de risco Cardiometabólico em Doentes com Psoríase

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ORIGINAL PAPER

Complement C3 as a marker of cardiometabolic risk in psoriasis

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Abstract Complement C3 is an emerging risk factor in metabolic and cardiovascular diseases. It is elevated in patients with cardiovascular disease, predicts future myocardial infarction, is closely related to insulin resistance and appears to be involved in atherogenesis. C3 levels have been associated with body fat. The aim of this study was to compare C3 levels in psoriasis patients and controls and to investigate within psoriasis patients the relationship between C3 levels with several measures of body fat, markers of cardiometabolic risk and subclinical atherosclerosis. Eighty adult patients with severe plaque-type psoriasis, without psoriatic arthritis or receiving systemic therapy/phototherapy in the previous 3 months, and 95 otherwise healthy patients were enrolled. Subjects with cardiovascular disease, other systemic inflammatory diseases, use of anti-inflammatory drugs or any infectious diseases in the 4 weeks prior to study enrollment were excluded. All subjects underwent clinical and laboratory evaluation and psoriasis patients underwent multidetector computed tomography scan for coronary artery calcification, abdominal fat and epicardial adipose tissue quantification. C3 levels were increased in psoriasis patients compared to controls (129.25 ± 20.92 vs 118.24 ± 17.86, $P < 0.001$), even after adjustment for age, sex and waist circumference ($P = 0.043$), indicating that this association was not solely mediated by the adipose tissue. Within psoriasis patients, C3 levels were independently associated with abdominal visceral fat, insulin resistance, metabolic syndrome and oxidized LDL-cholesterol, while C-reactive protein did not, showing that C3 may be a better marker of cardiometabolic risk than C-reactive protein. Although more studies are needed, C3 may be a useful marker of cardiometabolic risk in psoriasis.

Keywords Psoriasis · Complement C3 · Adiposity · Insulin resistance · Cardiometabolic risk · Metabolic syndrome

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Introduction

Complement 3 (C3) is an acute phase protein and important component of the complement pathways of the immune system [46] and is an emerging risk factor in obesity-related metabolic and cardiovascular diseases (CVD). Several studies have shown that C3 is elevated in patients with CVD, predicts future myocardial infarction, is closely related to insulin resistance and is associated with increased risk of type-2 diabetes [14–16, 21]. It is well

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known that inflammatory processes play a key role in atherogenesis [20], and many studies suggest that complement activation is involved in this process. C3 has been shown to be present in the atherosclerotic plaque [50] and the complement system to be activated in the atherosclerotic lesions [35]. Moreover, it appears to be a stronger inflammatory marker of insulin resistance and future coronary events than C-reactive protein (CRP) [9, 32]. C3 is mainly produced by the liver, but it is also synthesized by activated macrophages and adipocytes [34], therefore, behaving as an inflammatory cytokine and an adipokine. C3 mRNA expression is increased in adipose tissue of obese compared with lean subjects [24], and systemic C3 concentrations have been associated with several measures of body fat, such as body mass index (BMI), waist circumference (WC) and visceral and subcutaneous adipose tissue on computed tomography [17]. Additionally, C3 levels appear to decrease with weight loss [33].

Psoriasis is currently considered a systemic inflammatory disorder associated with numerous medical comorbidities and with clinically significant increased risk of CVD and cardiovascular mortality [22, 30, 38, 39]. The increased inflammatory load of these patients may play an important role in the accelerated atherosclerosis observed in psoriasis [3, 18, 26]. Mainly severe psoriasis is associated with a systemic and chronic inflammatory state characterized by an increased production of pro-inflammatory cytokines (TNF-α, INF-γ, IL-1β, IL-6, IL-17), adipokines (leptin, resistin) and inflammatory biomarkers, such as CRP, that generate a spectrum of pro-atherogenic changes. Obesity has been associated with and considered detrimental for psoriasis [2]. It is associated with persistent low-grade inflammation, particularly abdominal obesity, which is caused by excess accumulation of visceral adipose tissue that functions as an endocrine organ, releasing pro-inflammatory cytokines and adipokines [13]. Psoriasis has been independently associated with increased amount of visceral fat [4]. Data on the role of complement in psoriasis are scarce in the literature, but it is probably involved in psoriasis pathophysiology. Early studies have shown elevated serum C3 levels and complement activation in psoriasis patients and recently that C3 is expressed in psoriatic skin lesions [1, 41, 42]. Moreover, also in psoriatic arthritis, C3 levels have been shown to be increased, to correlate with disease activity and to decrease with anti-TNF-a therapy [10, 11].

The aim of this study was to compare serum C3 levels in psoriasis patients and controls and to analyze if eventual differences were independent of excess adiposity, using waist circumference as an indicator of visceral adipose tissue accumulation. Furthermore, to investigate within psoriasis patients, the relationship between C3 levels with several measures of body fat, other markers of cardiometabolic risk and subclinical atherosclerosis is assessed by coronary artery calcification (CAC) quantification.

Methods

In this cross-sectional study, adult patients with severe plaque-type psoriasis (PASI >10) consecutively observed at our psoriasis center were enrolled. The control group consisted in patients consecutively referred to the Dermatology outpatient clinic for conditions, such as nevi, other benign skin tumors or skin infections (tinea/warts). All patients were older than 18 years. Exclusion criteria for the psoriasis group were the presence of psoriatic arthritis (previous/current signs/symptoms of joint evolvement) and systemic therapy/phototherapy for at least 3 months before study enrollment. Patients being treated with topical therapy (corticosteroids or vitamin D analogs) were not excluded. Considered for both groups were the presence of CVD defined as the presence of coronary heart disease (CHD) (myocardial infarction, angina, angioplasty or coronary artery bypass grafting), cerebrovascular accident (stroke or transient ischemic attack) or peripheral vascular disease, the presence of other systemic inflammatory disease (lupus erythematous, rheumatoid arthritis or other spondyloarthropathies), the use of anti-inflammatory drugs and a positive history of any infectious diseases in the 4 weeks prior to study enrollment.

All subjects underwent clinical and laboratory evaluation. The following information was systematically recorded: demographic characteristics, medical history of cardiovascular risk factors (CVRF) and concomitant therapy. Patients were considered to have diabetes, hypertension or hyperlipidaemia if they were receiving specific treatment or had previously been diagnosed or if they had fasting plasma glucose ≥126 mg/dL, blood pressure ≥140/≥90 mmHg and fasting LDL-cholesterol ≥160 mg/dL or triglycerides ≥200 mg/dL, respectively. Overweight and obesity were defined by a BMI ≥25 or BMI ≥30, respectively, smoking status as current smokers (current tobacco use or stop smoking within the last year), non-smokers and ex-smokers (smoking cessation for more than a year) and family history of premature CHD (CHD in male first degree relative <55 years and in female first degree relative <65 years). Cardiovascular risk was assessed using Framingham risk score [48] and metabolic syndrome (MetS) was defined using NCEP ATPIII definition [19]. In the psoriasis group, psoriasis characteristics (family history, disease duration and previous treatments) and severity (according to PASI) were also recorded. Blood tests included fasting glucose and insulin, leptin, C3, high-sensitivity CRP (hs-CRP) and fasting serum lipids [total

cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, oxidized low-density lipoprotein cholesterol, triglycerides, apolipoprotein B, lipoprotein(a)]. Homeostasis model assessment (HOMA) was used to evaluate insulin resistance using the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L)/22.5 [8, 28].

Psoriasis patients underwent multidetector computed tomography (MDCT) scan for CAC, abdominal fat and epicardial adipose tissue (EAT) quantification. The 64-slice CT scanner (Somaton Sensation 64, Siemens Medical Solutions, Forchheim, Germany) used included 2 different acquisitions: one for abdominal fat quantification [abdominal visceral fat (AVF) and abdominal subcutaneous fat (ASF)], and the other for CAC and EAT assessment. The scan parameters and used methods have been previously described [5].

Mean radiation exposure was estimated as proposed by the European Working Group for Guidelines on Quality Criteria in CT [7].

The study was approved by the Hospital Institutional Review Board and all subjects gave written informed consent for use of their data.

Statistical analysis

Variables were tested for normality using Kolmogorov–Smirnov test. Descriptive statistics are presented as percentage for categorical variables and mean ± standard deviation or median with interquartile range (IQR) according to the distribution of the continuous variables. Log transformation was performed for non-normal variables. Patients and control subjects were compared using Student's *t* test for continuous variables and Chi-squared test for categorical variables. The independent association between disease status (psoriasis/control) and C3 levels was assessed using multivariable linear regression models with adjustment for age, sex, and in separate models with additional adjustment for WC or presence of MetS. Among psoriasis patients, the relationship between C3 and hs-CRP levels and clinical, laboratory and imaging variables was evaluated using Pearson's correlation coefficients (bivariate relationships) and multivariate linear (adjusting for age, sex and WC).

The level of statistical significance was set at $\alpha = 0.05$.

Statistical analyses were performed with SPSS version 21 (SPSS IBM, New York, USA).

Results

A total of 80 psoriasis patients and 95 controls were studied, with both groups being similar in terms of age and sex. The mean psoriasis duration was 22.3 ± 11.6 years, 42.5 % had family history of the disease, and mean PASI was 15.4 ± 7.0. Concerning CVRF and MetS syndrome, psoriasis patients were more likely to be obese ($P = 0.002$), to have hypertension ($P = 0.045$) and MetS ($P = 0.002$) compared to controls. Clinical indicators of excess adiposity, such as BMI and WC, were also significantly higher in psoriasis patients than in the control group ($P < 0.001$) (Table 1).

Table 1 Demographic and clinical characteristics of the study population

	Psoriasis	Controls	*P*
N	80	95	
Male	66.3 %	62.1 %	0.636
Age (years)	48.06 ± 10.70	48.44 ± 11.95	0.827
Psoriasis duration (years)	22.3 ± 11.6	–	–
Family history	42.5 %	–	–
PASI	15.4 ± 7.0	–	–
Psoriasis therapy[a]		–	–
Topical only	23.8 %	–	–
Ever phototherapy	52.5 %	–	–
Ever conventional systemic therapy[b]	60 %	–	–
Ever biologic therapy	2.5 %	–	–
Weight (kg)	80.59 ± 16.55	73.10 ± 14.13	**0.001**
Height (m)	1.67 ± 0.10	1.68 ± 0.09	0.426
Body mass index (kg/m^2)	28.93 ± 5.26	25.84 ± 4.07	**<0.001**
Waist circumference (cm)	97.33 ± 13.10	89.16 ± 11.63	**<0.001**
Systolic blood pressure (mmHg)[c]	129.11 ± 12.85	127.69 ± 13.39	0.547
Diastolic blood pressure (mmHg)[c]	78.39 ± 7.80	78.03 ± 9.06	0.813
Hypertension	47.5 %	32.6 %	**0.045**
Hypertensive therapy	32.5 %	21.1 %	0.087
Diabetes	13.8 %	6.3 %	0.098
Diabetes therapy	12.5 %	6.3 %	0.157
Hyperlipidemia	57.5 %	45.3 %	0.107
Statin therapy	23.8 %	14.7 %	0.129
Fibrate therapy	3.8 %	1.1 %	0.234
Obesity	38.8 %	17.9 %	**0.002**
Tobacco use	18.8 %	20 %	0.953
Family history CVD	11.3 %	10.5 %	0.878
Metabolic syndrome	35 %	14.7 %	**0.002**
Framingham risk score	8.76 ± 7.16	8.08 ± 5.75	0.584

Bold values indicate $P < 0.05$

[a] Patient could be in more than one group

[b] Includes acitretin, cyclosporine, methotrexate

[c] Excluding patients receiving treatment for hypertension

The laboratory features of the subjects are shown in Table 2. C3 and hs-CRP levels were significantly higher in psoriasis patients as compared with controls. Adjusting for age, sex and WC, as a marker of excess adiposity, and particularly abdominal visceral adipose tissue accumulation, C3

Table 2 Laboratory features of the study population

	Psoriasis	Controls	*P*	*P**	*P*+
C3 (mg/dL)	129.25 ± 20.92	118.24 ± 17.86	**<0.001**	**0.043**	**0.006**
hs-CRP (mg/dL)	2.56 (0.96–5.49)	1.57 (0.73–3.30)	**0.011**	0.272	0.053
Total cholesterol (mg/dL)[a]	206.80 ± 37.91	206.60 ± 39.23	0.976	0.686	0.566
HDL-cholesterol (mg/dL)[a]	48.0 (41.25–59.0)	54.0 (44.0–61.0)	0.434	0.724	0.904
LDL-cholesterol (mg/dL)[a]	129.14 ± 36.98	129.41 ± 34.11	0.964	0.771	0.489
OxLDL-cholesterol (mg/dL)[a]	174.20 ± 53.53	154.29 ± 58.32	**0.041**	**0.08**	**0.013**
VLDL-cholesterol (mg/dL)[a]	25.88 ± 16.51	22.91 ± 11.54	0.447	0.845	0.697
Triglycerides (mg/dL) [a]	107.00 (72.25–161.25)	99.0 (74.0–144.0)	0.745	0.433	0.365
ApoB[a]	93.12 ± 24.30	99.18 ± 27.06	0.176	0.251	0.173
Lp(a)[a]	21.0 (6.0–41.0)	22.0 (9.0–41.0)	0.875	0.948	0.907
Leptin	0.61 (0.40–1.97)	0.53 (0.30–1.10)	0.159	0.528	0.281
Glucose (mg/dL)	88.5 (81.0–100.0)	90.0 (81.0–96.0)	0.611	0.243	0.469
HOMA[b]	2.34 (1.48–4.03)	1.88 (1.42–2.72)	0.173	0.633	0.458
HOMA >2.5[b]	41.4 %	27.0 %	0.071	0.930	0.303

Bold values indicate $P < 0.05$

Log transformation was performed for non-normal variables prior to analysis

* Age-, sex- and waist circumference-adjusted

\+ Age-, sex,-metabolic syndrome-adjusted

[a] Excluding patients receiving hyperlipidemia treatment

[b] Excluding diabetic patients

levels continued to be significantly higher in psoriasis patients than in controls, being on average 5.76 ± 2.83 mg/dL higher ($P = 0.043$), while the difference between groups in hs-CRP levels did not persist after the multivariate adjustment. Similar results were found with adjustment for MetS.

Concerning lipid profile, and excluding patients receiving statins/fibrates, no significant difference between psoriasis patients and control subjects was found except for oxidized LDL (oxLDL) levels that were remained significantly higher in psoriasis patients than in controls after adjustment for age, sex and WC ($P = 0.028$) or MetS ($P = 0.013$). No significant differences between groups were found regarding insulin resistance (measured by HOMA or HOMA >2.5) and leptin levels.

Table 3 shows the relationship, within psoriasis patients, between C3 and hs-CRP levels and the clinical, laboratory and imaging parameters investigated in this study. C3 and hs-CRP levels were significantly and positively correlated with all clinical and imaging measures of body fat (Weight, BMI, WC, AVF and ASF) except for EAT to which only C3 was significantly correlated. Adjusting for age, sex and WC, C3 and hs-CRP remained associated exclusively with AVF ($P = 0.007$ and $P = 0.027$, respectively). Patients with MetS had significantly higher C3 and hs-PCR levels than those without ($P = 0.001$, $P = 0.043$, respectively); however, after adjusting for age, sex and WC, only C3 was associated with MetS ($P = 0.049$). Using HOMA value >2.5 as a marker of insulin resistance, C3 levels were higher in psoriasis patients with insulin resistance than those without, independently of age, sex and WC ($P = 0.030$), and a trend toward increased HOMA was also observed ($P = 0.056$). Increased levels of hs-CRP were not associated with insulin resistance and hs-CRP did not correlate with HOMA adjusting for age, sex and WC. Regarding lipid profile, C3 levels were significantly correlated with oxLDL, independently of age, sex and WC, exclusively with oxLDL ($P = 0.028$), while no association was found for hs-CRP. No association was found between C3 and hs-CRP levels and subclinical atherosclerosis (CAC >0) neither with disease severity and psoriasis duration.

Discussion

The major finding of this study is that C3 levels were increased in psoriasis patients compared to control subjects, independently of the excess adiposity observed in those patients, indicating that this association is not solely mediated by the adipose tissue. Moreover, within psoriasis patients, C3 levels were independently associated with AVF, insulin resistance, MetS and oxLDL, while CRP did not, showing that C3 may be a better marker of cardiometabolic risk than CRP.

Several inflammatory proteins have been evaluated as predictive biomarkers for CVD, and CRP has been the most widely studied and has consistently been shown to predict the development of CVD [36, 40]. The elevation of CRP among psoriasis patients has been extensively studied and linked to the excess cardiovascular risk associated with the disease [6]. However, CRP levels are not elevated specifically in CVD as a wide variety of stimuli including acute and chronic infection can be inducers. Recently, C3 has been independently associated with myocardial infarction after accounting for CRP, fibrinogen and CVRF, while CRP was not if accounting for C3 and the remaining variables [9]. In another study, patients undergoing carotid endarterectomy were followed-up for a median of

Table 3 Association between C3 and hs-CRP levels with clinical, laboratory and imaging variables within psoriasis patients

	C3			hs-CRP		
	r	*P*	*P**	*r*	*P*	*P**
Male	–	0.612	–	–	0.198	–
Age (years)	0.106	0.349	–	0.159	0.159	–
Weight (kg)	0.319	**0.004**	0.833	0.251	**0.024**	0.585
Height (m)	−0.083	0.464	0.253	−0.161	0.154	0.271
Body mass index (kg/m^2)	0.405	**<0.001**	0.401	0.383	**<0.001**	0.607
Waist circumference (cm)	0.409	**<0.001**	–	0.384	**<0.001**	–
Systolic blood pressure (mmHg)[a]	0.292	**0.032**	0.113	0.256	0.061	0.070
Diastolic blood pressure (mmHg)[a]	0.123	0.374	0.302	−0.051	0.716	0.916
Hypertension	–	0.115	0.402	–	0.080	0.350
Diabetes	–	0.536	0.160	–	0.099	0.949
Hyperlipidemia	–	0.150	0.373	–	0.445	0.852
Obesity	–	**<0.001**	0.162	–	**0.002**	0.567
Tobacco use	–	**0.041**	0.261	–	0.318	0.879
Family history CVD	–	0.642	0.847	–	0.971	0.782
Metabolic syndrome	–	**0.001**	**0.049**	–	**0.043**	0.631
Framingham risk score	0.166	0.146	0.237	0.179	0.117	0.269
Coronary artery calcification >0	–	0.445	0.844[+]	–	0.426	0.826[+]
Epicardial adipose tissue	0.262	**0.021**	0.116	0.115	0.319	0.881
Abdominal visceral fat	0.445	**<0.001**	**0.007**	0.385	**0.001**	**0.027**
Abdominal subcutaneous fat	0.349	**0.002**	0.470	0.337	**0.003**	0.371
C3 (mg/dL)	–	–	–	0.572	**<0.001**	**<0.001**
hs-CRP,	0.572	**<0.001**	**<0.001**	–	–	–
Total cholesterol (mg/dL)[b]	0.100	0.445	0.261	−0.024	0.856	0.949
HDL-cholesterol (mg/dL)[b]	−0.139	0.284	0.836	−0.114	0.386	0.577
LDL-cholesterol (mg/dL)[b]	0.009	0.947	0.593	−0.028	0.832	0.836
OxLDL-cholesterol (mg/dL)[b]	0.205	0.113	**0.028**	−0.061	0.641	0.913
VLDL-cholesterol (mg/dL)[b]	0.286	**0.025**	0.161	0.039	0.766	0.700
Triglycerides (mg/dL)[b]	0.364	**0.004**	0.071	0.059	0.651	0.597
ApoB[b]	0.106	0.416	0.380	0.003	0.984	0.850
Lp(a)[b]	−0.006	0.964	0.885	0.125	0.337	0.249
Leptin	0.283	**0.011**	0.640	0.303	**0.006**	0.773
Glucose (mg/dL)	0.157	0.164	0.747	0.149	0.188	0.863
HOMA[c]	0.441	**<0.001**	0.056	0.170	0.163	0.808
HOMA >2.5[c]	–	**<0.001**	**0.030**	–	0.286	0.601
Psoriasis duration (years)	−0.129	0.255	0.088	−0.087	0.443	0.105
PASI	0.106	0.350	0.445	0.145	0.200	0.190

Bold values indicate $P < 0.05$

* Age-, sex- and waist circumference-adjusted

+ Age-, sex- and cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, obesity, Tobacco use and family history CVD)-adjusted

[a] Excluding patients receiving hypertensive therapy

[b] Excluding patients receiving with statins/fibrates

[c] Excluding diabetic patients

14 months and C3 concentrations were found to predict restenosis, whereas CRP did not [43]. Therefore, C3 may be a more specific marker of CVD risk than CRP.

Although the association of body fat with C3 is clear, in this study psoriasis was associated with increased levels of C3, independently of WC, an indirect but reliable marker of excess adiposity, particularly visceral adipose tissue accumulation, postulated to have stronger associations with CHD biomarkers and a stronger predictor of CHD risk than BMI [25]. Thus, this association is probably not only mediated by the excess adipose tissue observed in psoriasis patients. Several pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and INF-γ have been shown to increase the production of C3 in many cell types, including the liver [45]. Although this stimulatory effect on adipocyte C3 production has not been clearly demonstrated, mRNA expression of C3 was shown to be increased by those cytokines in cultured mouse adipocytes and human pre-adipocytes [37, 50]. Therefore, these pro-inflammatory cytokines that are systemically and chronically increased in psoriasis may increase C3 production from the liver and probably from adipose tissue in psoriasis patients. Another

possible explanation may be the acylation stimulating protein (ASP) resistance in adipocytes caused by TNF-α. C3 is the precursor protein for ASP and TNF-α has been shown to cause a downregulation of ASP receptor, interfering with downstream ASP signalling [49]. Finally, also keratinocytes in psoriatic lesions have been shown to produce C3, being another possible source of C3 in psoriasis. Keratinocyte C3 expression may have an important role, along with other proteins, as the heterodimeric complex S100A8–S100A9, also termed calprotectin, in the initial immune activation of psoriasis inflammation in response to several environmental insults, such as barrier breakdown and bacterial invasion, leading infiltrating immune cells to produce additional inflammatory cytokines, like IL-17, MCP-1, and RANTES that will further activate keratinocytes, consequently leading to an auto-amplification loop, which subsequently results in a chronic inflammatory state, as observed in psoriasis [42].

Within psoriasis patients, C3 showed to be a stronger marker of insulin resistance and MetS than CRP, independently of excess adiposity. In a study comparing four inflammatory markers (C3 and three other markers proved to be increased in psoriasis, CRP, ESR, leukocyte count), C3 was the inflammatory marker that most strongly correlated with insulin resistance and independently of the main indexes of obesity [32]. In another study, it was found that adjusting for WC the relationship between CRP and HOMA was greatly weakened [47]. Evidently, and differently from CRP, the association of C3 with insulin resistance is not mainly mediated by adipose tissue. A possible explanation is that C3 hepatic production is mainly induced by IL-1β and TNF-α, which may interfere with insulin receptor functioning, through its phosphorylation and proteasomal degradation [27], causing insulin resistance, while CRP synthesis is stimulated by IL-6 produced in the adipose tissue and may mainly reflect the important contribution of obesity rather than provide a significant independent contribution to insulin resistance [32]. Another possibility is that C3 levels may parallel insulin resistance but not coinciding with it. The main activation fragment of C3, the ASP, is provided with insulin-like properties. Therefore, similarly to the increase in insulin levels in the presence of insulin resistance, a hypothetical ASP resistance could induce an increase in its precursor C3 [12].

The pathophysiologic role of C3 in metabolic syndrome remains unclear, but it has been stated that C3 concentrations may play an important role in its expression and to be an independent determinant of incident metabolic syndrome [44]. However, more studies, particularly population-based prospective studies, are needed to clarify whether C3 may help to identify psoriasis patients at risk of developing metabolic syndrome.

C3 levels were associated with all measurements of body fat, including AVF, ASF and EAT, a type of visceral adipose tissue surrounding the heart and coronary vessels, potentially relevant for the development of CHD due to local inflammation [29]. However, after adjusting to WC, it was associated exclusively with AVF, confirming that the visceral component of abdominal fat has more influence than the subcutaneous in the adipose tissue inflammation, while the association between C3 and EAT was not independent of visceral adiposity.

Psoriasis patients also presented significantly higher circulating oxLDL than controls and, within psoriasis patients, C3 was correlated with oxLDL, independently of WC. OxLDL has been found to amplify several CVD risk factors, triggering a chronic inflammatory reaction, resulting in a more vulnerable plaque, prone to rupture and thrombosis. Recently, it has been shown that oxLDL positively regulates C3 gene expression and protein secretion in human macrophages [31].

Finally, although C3 has been suggested to be involved in atherosclerosis, the mechanism of C3 accumulation in atherosclerotic lesions is not well elucidated. At least in this cohort of psoriasis patients, no association between C3 concentration and CAC was shown.

Limitations

A major limitation of the present study is the cross-sectional study design, which does not allow drawing definitive conclusion on causality. The small sample may be another limitation of the study. The imaging method used to assess AVF, EAT and subclinical atherosclerosis is a strength of the current study, but it was only available for psoriasis patients. Although WC is a good clinical indicator of visceral fat accumulation [23], MDCT assessment of AVF is the most reliable technic to assess it.

Conclusion

Serum C3, an important inflammatory marker of cardiovascular and cardiometabolic disorders, was increased in psoriasis. The excess adiposity, particularly visceral adiposity observed in these patients, surely plays a role, but the systemic inflammatory load of psoriasis probably increases the expression of C3 enhancing the risk of CVD. Moreover, C3 levels showed to have a stronger association with insulin resistance, metabolic syndrome and oxidized LDL-cholesterol than CRP. Although more studies are needed, C3 could be applied as a useful marker of cardiometabolic risk in psoriasis.

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Gordura Epicárdica e Calcificação Arterial Coronária em Doentes com Psoríase

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ORIGINAL ARTICLE

Epicardial adipose tissue and coronary artery calcification in psoriasis patients

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Abstract

Background Psoriasis is a chronic, immune-mediated disease associated with several cardio-metabolic comorbidities, accelerated atherosclerosis and cardiovascular disease (CVD). Other causes beyond systemic inflammation and traditional cardiovascular risk factors (CVRF) may be implicated in the increased risk of CVD observed in these patients. Epicardial adipose tissue (EAT), a type of visceral adipose tissue surrounding the heart and coronary vessels has been implicated in the development of coronary artery disease, by endocrine mechanisms, but particularly by local inflammation.

Objective To compare EAT volumes in psoriasis patients and controls using multidetector computed tomography (MDCT) and to analyse if eventual differences were independent from abdominal visceral adiposity; to determine, within psoriasis patients, its relation with subclinical atherosclerosis and other markers of cardiometabolic risk.

Methods One hundred patients with severe psoriasis, without CVD underwent MDCT, with EAT and abdominal visceral fat (AVF) assessment and coronary artery calcification (CAC) quantification and were compared with 202 control patients.

Results EAT volume was increased in psoriasis patients compared to control subjects, independently from age, sex and AVF, being, on average, 15.2 $\pm$ 4.41 mL higher (95% CI: 6.5–26.0, $P = 0.001$) than in controls. Moreover, psoriasis patients had a statistically significant higher risk of having subclinical atherosclerosis (OR 2.52, 95% CI: 1.23–5.16) than controls, after adjusting for traditional CVRF. Within psoriasis patients EAT volume was associated with subclinical atherosclerosis, independently of age, sex, psoriasis duration, classical CVRF and AVF.

Conclusion This study showed that psoriasis was associated with increased EAT volume independently of visceral abdominal fat and with subclinical atherosclerosis. Within psoriasis patients EAT volume was independently associated with CAC. EAT may be another important contributor to the higher cardiovascular risk observed in psoriasis.

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Conflicts of interest

None declared.

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Introduction

Psoriasis is a chronic inflammatory disease affecting 1–3% of the population.[1] Nowadays, it is considered as a systemic inflammatory disorder[2] associated with numerous medical comorbidities and with clinically significant increased risk of cardiovascular disease (CVD) and cardiovascular mortality.[3–6] Psoriasis appears to be an independent risk factor for subclinical atherosclerosis, probably due to disease's inflammatory burden, as an increased prevalence of subclinical atherosclerosis has been reported in several studies using various surrogate markers of atherosclerosis.[7–9] However, other causes beyond systemic inflammation and traditional cardiovascular risk factors (CVRF) may be implicated

in CVD in psoriasis. Psoriasis patients are more likely to have abdominal visceral adiposity than healthy subjects of similar waist circumference[10] which is strongly related to several cardiometabolic risk factors.[11]

Epicardial adipose tissue (EAT) is a type of visceral adipose tissue surrounding the heart and coronary vessels. It is externally limited by the pericardium and is mainly present in the atrioventricular and interventricular grooves, following the courses of the main coronary vessels[12](Fig. 1). Its close relation to the coronary tree has been suggested to be potentially relevant for the development of coronary artery disease (CAD), by endocrine mechanisms, but particularly by local inflammation and paracrine mechanisms, as EAT has been shown to produce and secrete, several proatherogenic and proinflammatory hormones and cytokines, including TNFα, IL-6, adipocytokines and leptin.[13–15] EAT has been independently associated with CAD[16] and in the Multi-Ethnic Study of Atherosclerosis (MESA) it has been shown to be predictive of incident cardiovascular events independently of conventional risk factors and body mass index (BMI).[17] There are various imaging modalities for measuring EAT, like magnetic resonance imaging (MRI), computed tomography (CT) and echocardiography, although MRI and CT are considered currently gold standard and additionally permit measuring abdominal visceral fat (AVF).[18]

The aim of this study was to compare EAT volumes in psoriasis patients and controls using multidetector computed tomography (MDCT) and to analyse if eventual differences were independent from AVF, a reliable marker of visceral adipose tissue accumulation, or other potential confounders, and to determine, within psoriasis patients, its relation with subclinical atherosclerosis using coronary artery calcification (CAC) quantification and other markers of cardiometabolic risk.

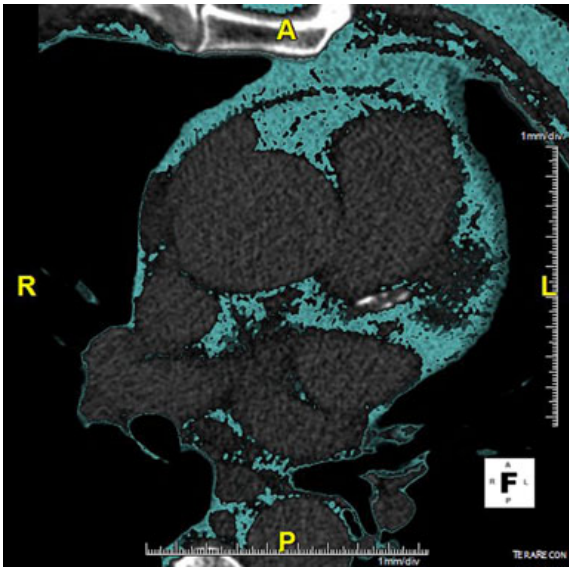

Figure 1 Multidetector computed tomography image of epicardial adipose tissue and left anterior descending coronary artery calcification.

Methods

Consecutive patients with severe plaque-type psoriasis [Psoriasis Area Severity Index (PASI) > 10 and/or systemic therapy], without psoriatic arthritis (no previous/current signs/symptoms of joint involvement) and no CVD, defined as the presence of coronary heart disease (CHD) (myocardial infarction, angina, angioplasty or coronary artery bypass grafting), cerebrovascular accident (stroke or transient ischemic attack) or peripheral vascular disease, were recruited from the Dermatology outpatient clinic. All patients underwent clinical evaluation (complete medical history and physical examination) and laboratory evaluation. The following information was systematically recorded: demographic characteristics, psoriasis disease duration, severity and current therapy, medical history of CVRF and therapy. Patients were considered to have diabetes, hypertension, hyperlipidaemia if they were receiving specific treatment or have been previously diagnosed or if they had fasting plasma glucose ≥126 mg/dL, blood pressure ≥ 140/≥90 mmHg and fasting low-density lipoprotein (LDL)-cholesterol ≥ 160 mg/dL or triglycerides ≥ 200 mg/dL respectively. Overweight and obesity was defined by a BMI≥25 or BMI≥30, respectively, smoking status as current smokers (current tobacco use or stop smoking within the last year), non-smokers and ex-smokers (smoking cessation for more than a year) and family history of premature CHD as history of CHD in male first degree relative <55 years and in female first degree relative <65 years. Cardiovascular risk was assessed using Framingham risk score[19] and metabolic syndrome (MS) was defined using National Cholesterol Education Program-Adult Treatment Panel (NCEP ATPIII) definition.[20] Blood tests included fasting glucose and insulin, haemoglobin A1c, leptin, complement C3 (C3), high-sensitivity C-reactive protein (hs-CRP) and fasting serum lipids.

Controls were retrospectively obtained from a cohort of 3321 consecutive patients referred to MDCT in a Cardiology Department, for non-invasive assessment of CAD or CVD risk assessment, during a 4-year period (2009–2013). Asymptomatic patients, patients with atypical clinical symptoms that was not confirmed CHD and patients referred for CVD risk assessment were selected, whereas patients with symptoms compatible with CAD or known CVD were excluded. Patients with diagnosis of psoriasis or other autoimmune diseases were also excluded. Available clinical data consisted in demographic characteristics and diagnosis of CVRF.

The study was approved by the hospital Institutional Review Board and all subjects gave written informed consent for use of their data.

Multidetector computed tomography acquisition

All patients underwent MDCT scan using a 64-slice CT scanner (Somaton Sensation 64; Siemens Medical Solutions, Forchheim, Germany), including two different acquisitions: one for abdominal fat quantification, and the other for CAC and EAT assessment.

Abdominal fat assessment

To assess abdominal fat, an abdominal single slice CT scan between L4 and L5 was performed, as described by Borkan.[21] The abdominal fat distribution was measured using a cursor pointer to trace the AVF area by delineating the abdominal wall muscular layer[22] and adipose tissue was identified in the areas with attenuation values ranging from −150 to −50 Hounsfield Units.[23] Total abdominal fat area was measured, and subcutaneous fat area was obtained by subtracting AVF from the total abdominal fat area.

Coronary artery calcification and epicardial adipose tissue quantification

The scan parameters used for CAC and EAT acquisition have been previously described.[24] CAC score was reported as the mean Agatston score and was calculated using a detection threshold of 130HU using semiautomated software (Syngo Calcium Scoring; Siemens Medical Solutions).[25]

Total EAT volume was quantified by an experienced radiographer using a cursor pointer to manually trace the pericardial contour, using 1-mm-thick reconstructed axial slices for every 10–20 mm starting from the lower visible level of pulmonary artery bifurcation until the last slice where pericardium was still visible.[24] The pericardium contour was extrapolated by the software (Syngo Volume, Siemens Medical Solutions) for the non-traced slices and rechecked by the operator. Within these limits, EAT was identified using the adipose tissue attenuation references. Mediastinal adipose tissue and pericardial adipose fat were excluded from analysis.

Radiation exposure

Mean radiation exposure was estimated by the method proposed by the European Working Group for Guidelines on Quality Criteria in CT.[26]

Statistical analysis

Descriptive statistics are presented as percentage for categorical variables and mean ± standard deviation, or median with interquartile range according to the distribution of the continuous variables. Variables were tested for normality using Kolmogorov–Smirnov test. Patients and control subjects were compared using Student's *t*-test and the Mann–Whitney *U*-test for normally and non-normally distributed continuous variables, respectively, and chi-squared test for categorical variables.

The independent association between disease status (psoriasis or control) and EAT volume was assessed using multivariable linear regression models with adjustment for age, sex, and in separate model with additional adjustment for AVF. In addition, a multivariable linear regression model was built with EAT as dependent variable. Variables which showed $P < 0.100$ in univariate analysis were candidates to be included in the multivariable linear regression model. The final multivariable linear regression model included only the variables found to be statically significant after adjusting for the remaining variables. The association between disease status and categorical variables was assessed using multivariable logistic regression model.

Among psoriasis patients, the relationship between EAT volume and clinical, laboratory and imaging variables was evaluated using Spearman's rank correlation coefficients (bivariate relationships) and multivariable linear regression (independent associations adjusting for age and sex, and additionally for AVF).

The level of statistical significance was set at $\alpha = 0.05$. Statistical analyses were performed with SPSS version 21 (SPSS IBM, New York, USA).

Results

A total of 100 psoriasis patients and 202 controls were studied Table 1. While there was no difference between both groups concerning gender, psoriasis patients were significantly younger than control subjects (47.4 ± 10.8 vs. 54.4 ± 10.1, $P < 0.001$).

The mean psoriasis duration was 21.9 ± 10.9 years, 43% had family history of the disease, mean PASI was 12.8 ± 8.0 and 84% of the patient were receiving or had previously received systemic therapy (21% were receiving anti-TNFα therapy).

No difference was found between groups concerning the prevalence of CVRF. After adjustment for age and sex, psoriasis patients had a higher risk of dyslipidaemia (OR 1.82, 95% CI:1.04–3.17) and being obese (OR 2.03, 95% CI:1.16–3.57).

Association of disease status with EAT volume and subclinical atherosclerosis

EAT volume was significantly larger in psoriasis patients than in controls independently of age, sex and AVF, being, on average 15.2 ± 4.41 mL higher (95% CI:6.5–26.0, $P = 0.001$) Table 2.

Based on the multivariable regression analysis, EAT volume was independently associated with psoriasis ($P = 0.002$), sex ($P < 0.001$), age ($P = 0.001$), AVF ($P < 0.001$) and total fat ($P = 0.023$). EAT volume of psoriasis patients was, on average, 13.6 ± 4.43 mL larger (95% CI:4.9–22.4) than in control subjects, adjusting for all the aforementioned variables Table 3.

Regarding the presence of subclinical atherosclerosis (CAC > 0), there was no difference between both groups ($P = 0.410$). Adjusting for age, sex and CVRF, psoriasis patients had a statistically significant higher risk of having subclinical atherosclerosis (OR 2.52, CI 95%:1.23–5.16). With further

Table 1 Characteristics of study subjects

	Psoriasis	Controls	*P*
N°	100	202	
Male	64%	64.4%	0.952
Age, year	47.4 ± 10.8	54.4 ± 10.1	<0.001
Body mass index, kg/m^2	28.6 ± 4.99	28.1 ± 4.17	0.346
Waist circumference, cm	95.8 ± 12.16	–	
Systolic blood pressure, mmHg	133.6 ± 16.14	–	
Diastolic blood pressure, mmHg	80.9 ± 8.87	–	
Hypertension	49%	52%	0.626
Diabetes	12%	15.8%	0.373
Dyslipidaemia	55%	55%	0.994
Obese	37%	27.6%	0.098
Smoker	21%	16.8%	0.377
Family history CV events	13%	15.3%	0.586
Metabolic syndrome	32%	–	
Framingham risk score (*n* = 97)	8.5 ± 7.15	–	
Psoriasis duration, y	21.9 ± 10.9	–	
Family history	43%	–	
PASI	12.8 ± 8.0	–	
Psoriasis therapy*			
Topical only	16%	–	
Ever phototherapy	61%	–	
Ever acitretin	30%	–	
Ever cyclosporine	51%	–	
Ever methotrexate	33%	–	
Ever biological therapy	21%	–	
Glucose, mg/dL	93.3 ± 28.3	–	
HgA1C, %	5.4 (5.2–5.6)	–	
Total cholesterol, mg/dL	206.5 ± 39.9	–	
Triglycerides, mg/dL	126.7 ± 72.6	–	
HDL-cholesterol, mg/dL	51.5 ± 13.2	–	
LDL-cholesterol, mg/dL	129.1 ± 38.2	–	
VLDL-cholesterol, mg/dL	22.0 (14.0-32.5)	–	
Oxidized LDL-cholesterol, mg/dL	183.4 ± 56.4	–	
ApoB, mg/dL	94.0 ± 24.3	–	
Lp(a), mg/dL	35.4 ± 40.3	–	
C3, mg/dL	127.2 ± 20.5	–	
hs-CRP, mg/dL	4.49 ± 7.06	–	
Leptin, mg/dL	1.1 ± 1.1	–	
HOMA	2.93 ± 2.3	–	
HOMA > 2.5	34.1%	–	

*Patient could be in more than one group.
ApoB, apolipoprotein B; C3, complement C3; HgA1C, haemoglobin A1c; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a); PASI, Psoriasis Area Severity Index.

adjustment for EAT and AVF, psoriasis patients still had a higher risk of having subclinical atherosclerosis (OR 2.34, CI 95%:1.12–4.93) Table 2.

Table 2 Adipose tissue and atherosclerosis assessment in psoriasis and control group

	Psoriasis	Controls	*P**	*P*†
Adipose tissue assessment				
Epicardial fat tissue	101.4 ± 55.52	92.2 ± 38.33	<0.001	0.001
Abdominal visceral fat	136.7 ± 84.02	141.5 ± 71.25	0.006	–
Subcutaneous fat	242.1 ± 108.85	203.6 ± 86.89	0.001	0.010
Total fat	378.8 ± 146.28	345.2 ± 124.09	<0.001	0.010
Atherosclerosis assessment		OR (95% CI)‡	OR (95% CI)§	
Presence of atherosclerosis (CAC > 0)	43% 48%	2.52 (1.23–5.16)	2.34 (1.12–4.93)	

*Age- and sex-adjusted *P*.
†Age-, sex- and AVF-adjusted *P*.
‡Age-, sex- and CVRF-adjusted odds ratio.
§Age-, sex-, CVRF-, EAT- and AVF-adjusted odds ratio.
AVF, Abdominal visceral fat; CAC, Coronary artery calcification; CVRF, Cardiovascular risk factors; EAT, Epicardial fat tissue.

Table 3 Independent association of epicardial adipose tissue and psoriasis

	Univariate analysis	Multivariable analysis
Psoriasis	0.097	0.002
Sex	<0.001	<0.001
Age	<0.001	0.001
Hypertension	0.001	
Diabetes	0.027	
Dyslipidaemia	0.001	
Obesity	0.001	
Tobacco use	0.489	
Family history of coronary heart disease	0.616	
Coronary artery calcification	<0.001	
Abdominal visceral fat	<0.001	<0.001
Subcutaneous fat	0.105	
Total fat	<0.001	0.023

Association of clinical, laboratory and imaging variables with EAT volume in patients with psoriasis

Within psoriasis patients, EAT volume was positively correlated with 21 different variables and negatively correlated with high-density lipoprotein (HDL)-cholesterol. Adjusting for age and sex, significant association with EAT volume remained only for diastolic blood pressure ($P = 0.039$), obesity ($P = 0.005$), BMI ($P = 0.001$), waist circumference ($P = 0.001$), waist-to-height ratio ($P = 0.013$), total fat ($P < 0.001$), subcutaneous fat

($P = 0.029$) and AVF ($P < 0.001$). With additional adjustment for AVF no variable remained significantly associated with EAT volume. No significant association between EAT volume and disease severity, psoriasis duration or current use or duration of TNFα inhibitor use was found ($P > 0.05$) Table 4.

EAT and subclinical atherosclerosis

Forty-three per cent of the patients had an Agatston score > 0. CAC levels were positively related with both EAT and AVF ($P < 0.001$). EAT volume was related to coronary atherosclerotic burden in psoriasis patients: it was significantly higher in patients with subclinical atherosclerosis than those without any degree of coronary calcification (135.7 ± 8.39 vs. 75.6 ± 5.29, $P < 0.001$), even after adjustment for age, sex, psoriasis duration, CVRF and AVF ($P = 0.004$), with EAT volume of patients with atherosclerosis being, on average, 31.6 ± 10.76 mL (95% CI:10.3–53.0) higher than in control subjects.

EAT and MS and insulin resistance

Patients with MS had a significantly higher EAT volume than those without MS ($P = 0.032$), however, after adjusting for age, sex and further to AVF there was no statistically significant difference. Using homeostatic model assessment (HOMA) value >2.5 as a marker of insulin resistance, EAT volume was larger in psoriasis patients with insulin resistance than those without after adjusting for age and sex ($P = 0.002$); no difference was found with further adjustment to AVF ($P = 0.130$). Similar results were observed analysing the association between HOMA and EAT.

EAT, inflammation and leptin

C3 was associated with EAT volume in univariate analysis ($P = 0.001$) and after adjustment for age and sex ($P = 0.003$). With further adjustment for AVF, there was no significant association ($P = 0.443$). Concerning hs-CRP and leptin, no association was observed in unadjusted or adjusted analysis.

Table 4 Association between clinical and laboratory measures and EAT volume in patients with psoriasis

	rho	P	P*	P†
Male Sex	–	<0.001	–	–
Age	0.509	<0.001	–	–
PASI	0.112	0.269	0.184	0.394
Psoriasis duration	0.016	0.877	0.669	0.493
Anti-TNFα use	–	0.186	0.687	0.438
Weight	0.517	<0.001	<0.001	0.277
Body mass index	0.426	<0.001	0.001	0.865
Waist circumference	0.512	<0.001	0.001	0.756
Waist-to-height ratio	0.374	<0.001	0.011	0.304
Systolic blood pressure	0.435	<0.001	0.054	0.785
Diastolic blood pressure	0.362	<0.002	0.039	0.776
Hypertension	–	0.011	0.419	0.522
Diabetes	–	0.265	0.929	0.190
Dyslipidaemia	–	0.016	0.455	0.103
Obesity	–	0.012	0.005	0.988
Tobacco use	–	0.221	0.067	0.319
Family history CVD	–	0.929	0.890	0.817
Metabolic Syndrome	–	0.032	0.215	0.543
Framingham risk score	0.559	<0.001	0.598	0.945
Abdominal visceral fat	0.780	<0.001	<0.001	–
Subcutaneous fat	0.031	0.758	0.029	0.747
Total fat	0.478	<0.001	<0.001	0.747
CAC > 0	–	<0.001	0.001	0.004‡
C3	0.325	0.001	0.003	0.443
hs-CRP	0.141	0.163	0.348	0.436
Leptin	0.095	0.348	0.063	0.908
Glucose	0.419	<0.001	0.971	0.172
HA1C	0.283	0.004	0.950	0.185
HOMA	0.468	<0.001	0.045	0.906
HOMA > 2.5	–	<0.001	0.002	0.130
Total cholesterol	0.056	0.578	0.434	0.765
Triglycerides	0.386	<0.001	0.259	0.476
HDL-cholesterol	−0.253	0.011	0.742	0.610
LDL-cholesterol	0.004	0.971	0.267	0.838
VLDV-cholesterol	0.369	<0.001	0.388	0.467
Oxidized LDL-cholesterol	0.172	0.087	0.294	0.519
ApoB	0.174	0.144	0.359	0.377
Lp(a)	−0.074	0.462	0.486	0.664

*Age- and sex-adjusted *P*.
†Age-, sex- and AVF-adjusted *P*.
‡Age-, sex-, CVRF-, psoriasis duration- and AVF-adjusted *P*.
ApoB, apolipoprotein B; AVF, abdominal visceral fat; C3, complement C3; CAC, coronary artery calcification; CVRF, cardiovascular risk factors; HgA1C, haemoglobin A1c; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a).

Discussion

The major finding of this study is that EAT volume is increased in psoriasis patients comparing to control subjects, independently from AVF, a reliable and better marker of excess visceral adiposity than indirect measures such as BMI or waist circumference. Moreover, within psoriasis patients, EAT volume was associated with subclinical atherosclerosis, evaluated with CAC, in an independent way from age, sex, psoriasis duration, CVRF and AVF. It was also found that psoriasis was independently associated with coronary atherosclerosis, independently of age, sex, CVRF, EAT volume and AVF, confirming previous studies appointing that psoriasis may be an independent risk factor of atherosclerosis.[7,27]

This is the first time that, in severe psoriasis patients, EAT, a potential relevant factor for the development of CAD, is proven to be independently associated with coronary atherosclerotic burden, as assessed by CAC, even when adjusted to the confounders mentioned above, particularly AVF. These findings provide another possible link between psoriasis and atherosclerosis.

Recently, researchers have shown EAT as an endocrine organ that can produce and secrete several proatherosclerotic and pro-inflammatory hormones and cytokines, including IL-6, TNFα, leptin, MCP-1 and free fatty acids.[12] Although EAT represents only 1% of the total body fat mass in physiological conditions, it may be particularly important in the pathophysiology of atherosclerosis, mediated through its metabolic effects both at a paracrine level, through inflammatory burden proximal to the coronary arteries, and at a systemic level, as EAT secretes more inflammatory cytokines than subcutaneous fat.[13,14] EAT has been implicated in subclinical atherosclerosis,[25] CAD and in the risk of future adverse cardiovascular outcome[17,28] as well as with insulin resistance, diabetes and MS.[19,29]

Measurement of EAT on cardiac imaging is highly reproducible and easily performed on the same images obtained for other proposes (in this case measurement of CAC). MDCT is a non-invasive technique for the diagnosis of CAD and allows simultaneous high-resolution volumetric quantification of EAT and AVF measurement. Moreover, volumetric quantification of EAT using cardiac CT has been shown to have superior reproducibility compared to thickness and area measurements, e.g. using transthoracic echocardiography.[30,31] Although it employs radiation, the exposure is minimum and no contrast administration is required. CAC score by CT is a non-invasive measure of subclinical atherosclerosis that has been shown to be a useful examination to evaluate the extent of coronary atherosclerosis and predict future cardiovascular events.[32] Nevertheless, it does not take into consideration the distribution of individual calcified lesions and cannot distinguish between plaques located in high-risk areas versus low-risk areas. In a prospective analysis of the MESA cohort, CAC showed to be a better predictor for CHD and total CVD than carotid intima-media thickness (CIMT).[33]

Recently, it has been showed an increased EAT thickness measured by transthoracic echocardiography[34,35] and MDCT[36] in psoriasis patients and, in one study, that EAT closely correlated with CIMT in psoriasis patients.[34] However, in addition to smaller study groups (31–60 patients), there was no measurement of AVF, to elucidate its relation with abdominal adipose tissue in psoriasis patients. Our study, analysing the relation between EAT, AVF and coronary calcification, aimed to study if psoriasis patients had larger EAT volume than control subjects, independently of AVF, and if EAT could be used as an independent predictor of coronary atherosclerosis in psoriasis patients. Its design was thought to test the independence of EAT and CAC from AVF. Our results are in line with previous publications which found a higher atherosclerotic burden in patients with higher volume of EAT.[16,17,28] Being so, an increased EAT volume, along with systemic inflammation and increased CVRF might be another cause implicated in CVD in psoriasis.

In this study, EAT volume was associated with several indirect measures of cardiovascular risk as BMI, waist circumference, waist-to-height ratio, diastolic pressure and obesity that was attenuated after adjusting for AVF. However, the relation between EAT and coronary atherosclerosis was found to be independent from AVF, suggesting that a different mechanism than overall visceral fat may be involved.

EAT volume was also associated with higher levels of C3 but not hs-CRP when adjusting for age and sex. With further adjustment for AVF, no association was found. Recently, C3 has been found to be independently associated with myocardial infarction and an independent determinant of incident cardiometabolic risk and to be a more specific marker than CRP.[37,38] Although EAT was not associated with markers of systemic inflammation independently of visceral adiposity, the possibility that there may be a local influence related to EAT cannot be excluded.

Finally, an association with insulin resistance was also found, that remained significant after adjustment for sex and age, but it was not independent of AVF, showing that EAT may be a marker and contributor of insulin resistance.

The reason EAT is increased in patients with psoriasis remains unknown, but probably it is multifactorial, with genetic, immune-mediated and behaviour factors having a role. It has been also shown to be increased in rheumatoid arthritis, another inflammatory condition associated with high risk of CVD.[39] EAT and psoriasis association is probably explained at a genetic level, due to shared genetic and immune-mediated mechanisms, with adipocytes and inflammatory-type macrophages contributing to both disease processes through secretion of several inflammatory mediators. Probably, similar to obesity,[40] higher volume of EAT co-exists with psoriasis, contributing to a poorer long-term clinical outcome of psoriasis as well as to an excess cardiovascular risk and other CVRF observed in psoriasis, such as insulin resistance or hypertension, due to the several adipocyte-derived hormones, adipokines and proinflammatory cytokines. Another possible cause is behavioural, as stigma and social avoidance usually present in psoriasis patients might make physical activity adherence problematic. Moreover, it has been shown that significant weight loss and aerobic exercise training may be associated with significant reduction in EAT thickness,[41,42] highlighting the importance of encouraging psoriasis patients to correct their modifiable CVRF, particularly obesity and to adopt healthy life-style behaviours such as regular physical activity. Thus, EAT is probably another important contributor to the higher cardiovascular risk observed in psoriasis, with particular importance due to the local effect on myocardial vascularization, whereas contributing and relating to the other cardiometabolic comorbidities observed in psoriasis.

Limitations and strengths

The imaging method used to assess EAT and subclinical atherosclerosis is a strength of this study. MDCT is, along with MRI, the gold standard to measure EAT. Furthermore, it also enables AVF quantification, a more reliable marker of excess adiposity.

In addition, a very sensitive and specific non-invasive measure of subclinical atherosclerosis was used, that has been shown to be a better predictor for CHD and total CVD than CIMT.[33]

Some limitations should be addressed. Despite being the largest study focussing on the EAT volume in psoriasis and its relation with CAC and other cardiometabolic markers, this is still a relatively small single centre study. Moreover, besides hs-CRP and C3, no other inflammatory markers or cytokines were assessed. Although the number of control subjects included in this study was considerable, they were not enrolled the same way as psoriasis patients. Available clinical variables were limited, whereas the psoriasis group was extensively evaluated. Finally, control subjects were recruited from a cohort of patients that, for some clinical reason, were referred to non-invasive assessment of CAD or CVD risk. Thus, even excluding all patients with known CVD or high clinical suspicion of CAD, it is difficult to consider these control patients as 'healthy subjects'. However, this population would have, at most, a higher risk of CVD than the general population.

Conclusion

This study showed an increased EAT volume and subclinical atherosclerosis in psoriasis patients comparing to control subjects, independently of AVF, using the gold standard and highly sensitive method of evaluating EAT, AVF and subclinical atherosclerosis. Moreover, within psoriasis patients, EAT was independently associated with coronary atherosclerotic burden providing another explanation for the increase risk of CVD in psoriasis. Further prospective studies are warranted to confirm this data.

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Comorbilidades Cardiovasculares na Psoríase em Idade Pediátrica

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Cardiovascular comorbidities in childhood psoriasis

Background: Psoriasis is a common, chronic, systemic inflammatory skin disease associated with numerous cardiovascular comorbidities. Much evidence of this association exists in the adult population, data available in childhood psoriasis is more limited. *Objectives:* To analyze the prevalence of excess adiposity, cardiovascular risk factors, metabolic syndrome and lipid profile in children with psoriasis comparing to control group with similar age and sex distribution. *Materials & methods:* A case-control study was conducted with children, 5-15 years-old, with moderate-to-severe plaque-type psoriasis and a control group comprising children with other skin diseases without systemic inflammatory diseases. *Results:* Psoriatic children had a significantly higher prevalence and greater odds of excess adiposity compared to controls: BMI ($\geq 85^{th}$ percentile; OR 4.4; 95%CI 1.2-15.6), waist circumference ($>75^{th}$ percentile; OR 7.4; 95%CI 2.0-27.7) and waist-to-height ratio (>0.490; OR 4.6; 95%CI 1.3-17.0). A higher prevalence of metabolic syndrome was observed in children with psoriasis compared to controls (25% *vs* 3.7%; $P = 0.07$), and two components of the metabolic syndrome were significantly higher in the psoriasis group: waist circumference (75% *vs* 29.6%; $P = 0.002$) and the high blood pressure component (30% *vs* 3.7% $P = 0.032$). Finally, an altered and more atherogenic lipid profile was observed among psoriatic patients without excess adiposity. *Conclusion:* This study demonstrates that comorbidities known to be associated with adult psoriasis are also observed in childhood psoriasis, reinforcing the need for screening cardiovascular comorbidities in children with psoriasis and promoting healthy lifestyle choices in these patients. Moreover, it also suggests that its association with psoriasis may be in part genetically determined rather than uniquely acquired.

Key words: cardiovascular comorbidities, childhood psoriasis, excess adiposity, lipid profile, metabolic syndrome, visceral adiposity

Psoriasis is a common chronic inflammatory skin disease that affects 1% to 3% of the general population [1]. While most patients report its negative impact on their quality of life, psoriasis appears to be more than skin deep. In fact, psoriasis is now considered a systemic inflammatory disorder associated with numerous medical comorbidities [2]. Large epidemiological studies have found that adult patients with psoriasis have increased prevalence of traditional cardiovascular (CV) risk factors such as diabetes, hypertension, dyslipidemia, obesity and metabolic syndrome compared with the general population [3, 4] and more importantly a clinically significantly increased risk of CV disease and CV mortality [5]. The connection between psoriasis, atherosclerosis and cardiovascular disease may be related to a common genetic basis, shared inflammatory pathways, including Th-1 and Th-17 mediated inflammation, alterations in angiogenesis and endothelial dysfunction [6, 7].

Data available on cardiovascular risk in childhood psoriasis is more limited, although there is increasing evidence that childhood psoriasis is also associated with an increased prevalence of cardiovascular comorbidities, especially obesity but also hypertension, diabetes, hyperlipidemia and metabolic syndrome [8-12].

The prevalence of childhood plaque-type psoriasis appears to be between 0.37% and 0.55% within the first decade of life and 1.01% to 1.37% within the second decade, showing that psoriasis is also a common disease in childhood [9, 13]. Children with psoriasis appear to be at increased risk of being overweight or obese and thus are at increased risk of complications related to excess adiposity, as it has been found that obesity may be 1.7 to 2.6-fold more frequent in psoriatic children than in controls [9, 14, 15]. Interestingly, it has also been shown that psoriasis severity may be associated with obesity [8]. On the other hand, overweight or obese children appear to be at increased risk of having psoriasis [16].

Concerning other cardiovascular risk factors, data is more limited. Augustin *et al* assessed the prevalence rate of comorbidities of juvenile psoriasis in Germany, based on

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health insurance data, and hyperlipidemia, diabetes and hypertension were twice as common in patients with psoriasis [8] while Au *et al* found a higher prevalence of metabolic syndrome in 20 children with psoriasis, although no statistically significant difference was found in body mass index or for any of the individual components of metabolic syndrome [10].
The aim of the present study was to analyse the prevalence of excess adiposity, particularly central/visceral adiposity, cardiovascular risk factors, metabolic syndrome and its components and lipid profile in a group of children with psoriasis, compared to a control group with a similar age and sex distribution.

Materials and methods

In this case control study, children aged between 5-15 years old, with moderate-to-severe plaque type psoriasis (BSA >5% and/or previous/current systemic therapy), without psoriatic arthritis, consecutively observed at our Psoriasis Centre, were enrolled. The control group was recruited from the same setting, during the same period and comprised children who attended the Dermatology Department for other skin diseases, such as eczema, acne or skin infections and required blood collection for their clinical condition workup. They had no psoriasis or family history of psoriasis/psoriatic arthritis or other systemic inflammatory diseases, such as rheumatoid arthritis, lupus erythematous or inflammatory bowel disease.
All psoriatic patients and controls underwent a thorough clinical and laboratory evaluation including complete medical history and physical examination. The following information was systematically recorded: demographic characteristics (age, sex), psoriasis age of onset, severity and treatment, height, weight, abdominal circumference and blood pressure were recorded, as well as determination of fasting plasma concentration of glucose, insulin, glycosylated hemoglobin and lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, oxidized LDL-cholesterol (ox-LDL), triglycerides, lipoprotein(a), apolipoprotein B (apoB)).
Body mass index (BMI) was calculated as weight in kilograms divided by height squared in meters. Children were classified as normal-weight ($<85^{th}$ percentile), overweight ($\geq 85^{th}$ and $<95^{th}$ percentile) and obese ($\geq 95^{th}$ percentile) [17]. Evaluation of central adiposity was performed using 2 sensitive, non-invasive surrogate markers of central adiposity: waist circumference (WC) and waist-to-height ratio. WC was determined using a measuring tape, positioned horizontally, parallel to the floor, between the top of the iliac crest and the lowest rib. Patients were classified into 6 percentile groups, according to sex, age and ethnicity cutoffs (Overweight and obesity were defined as WC $>75^{th}$ percentile and WC $>90^{th}$ percentile respectively) [18]. Waist-to-height ratio was used to estimate cardiovascular risk, classifying patients at high risk (≥ 0.539) and intermediate risk (≥ 0.490), using the cutoffs established by Kahn [19].
Hypertension was defined as systolic and/or diastolic BP $\geq$ the 95th age-, sex- and height-specific percentile [20] and dyslipidemia as LDL-C and/or triglycerides $\geq$ the 95th age-, sex-specific percentile and/or HDL-C $\leq$ the 5^{th} age-, sex-specific percentile [21]. Diabetes diagnosis was based on a fasting plasma glucose $\geq$ 126 mg/dL or HbA1c $\geq$ 6.5% [22] and insulin resistance was based on the homeostatic model assessment (HOMA), calculated as the product of the fasting plasma insulin level (in micro units per millilitre) and the fasting plasma glucose level (in millimoles per litre) divided by 22.5. HOMA>3.16 was considered insulin resistance and <3.16 as insulin sensitive [23].
For the definition of metabolic syndrome, the modified criteria of ATPIII proposed by de Ferranti was used, defined as the presence of 3 or more of the following criteria: waist circumference $\geq 75^{th}$ percentile for age and sex, triglycerides $\geq$100mg/dL, HDL-C <50mg/dL, fasting glucose $\geq$110 mg/dL and systolic or diastolic blood pressure greater than the 90^{th} percentile for age, gender and height [24].
The study protocol was approved by the Hospital Ethical Committee and all patients and controls agreed to participate.

Statistical analysis

Descriptive statistics are presented as counts and percentages for categorical variables and means ($\pm$ SDs) or medians (IQR) for continuous data. Distribution of continuous variables was tested for normality using the Kolmogorov-Smirnov test. The χ^2 test and Fisher exact test were used to compare categorical variables and the t-test or Mann-Whitney U test to compare continuous variables between groups. Odds ratios (OR) and the corresponding 95% confidence intervals (CI), were estimated. The independent associations between disease status (psoriasis and controls) and the clinical and analytical variables were assessed using multivariable logistic or linear regression models adjusting for age and sex as confounders.
The level of statistical significance was set at $\alpha = 0.05$. Statistical analyses were performed with SPSS version 21 (SPSS IBM, New York, U.S.A).

Results

This study included 20 psoriatic children and 27 controls. There was no difference between cases and controls for age (10.40 ± 3.15 years *vs* 10.4 ± 2.87 years, p = 0.993) and sex (female: 65% *vs* 66.7%, p = 0.905). Mean psoriasis duration time was 3.0 years ($\pm$ 1.11; 2-6 years); mean BSA was 7.2% ($\pm$ 3.66; 5-17%). Most psoriatic children were receiving topical therapy (90%), while 10% were on UVBnb phototherapy; 30% had already received previously systemic therapy (UVBnb phototherapy, cyclosporine, methotrexate and acitretin).
Descriptive characteristics of the study population are reported in *table 1*.
The mean BMI percentile was significantly higher among psoriatic patients (80.89 $\pm$ 18.42 *vs* 65.97 $\pm$ 23.36, p = 0.018). Compared to the control group, a significantly higher percentage of children with psoriasis were overweight or obese (35% *vs* 22.2% and 25% *vs* 3.7%; *P* = 0.03). The age- and sex-adjusted odds ratio (OR) for excess adiposity (overweight/obese) was 4.4 (95% CI 1.2-15.6). Although a higher proportion of children with psoriasis

Table 1. Characteristics of the study population

	Psoriasis	Controls	*P* value	*P* value*
Participants, No.	20	27		
Age, mean (SD), y	10.40 (3.15)	10.4 (2.87)	0.993	
Female sex (%)	65%	66.7%	0.905	
Psoriasis characteristics				
Psoriasis duration, mean (SD); min-max, y	3.0 (1.11); 2-6	. . .. .	. . .. .	
BSA, mean (SD); min-max, %	7.2% (3.66); 5-17	. . .. .	. . .. .	
Family history - 1st degree relative (%)	35%	. . .. .	. . .. .	
Current treatment (%)				
Topical	90%	. . .. .	. . .. .	
Systemic	10%	. . .. .	. . .. .	
Previous systemic treatment	30%	. . .. .	. . .. .	
Metabolic characteristics				
SBP, mm/Hg	107.1 (12.1)	105.1 (11.7)	0.579	0.507
DBP, mm/Hg	62.0 (9.2)	63.1 (8.3)	0.647	0.630
SBP percentile	59.2 (26.3)	49.3 (27.5)	0.224	0.212
DBP percentile	51.0 (25.5)	55.2 (24.1)	0.569	0.580
Weight	46.2 (16.3)	41.6 (13.9)	0.310	0.065
Height	145 (165)	146 (158)	0.919	0.818
BMI	21.1 (4.0)	19.0 (2.9)	**0.038**	**0.011**
BMI percentile	80.89 (18.42	65.97 (23.36)	**0.018**	**0.025**
BMI categories (%)				
Normal weight	40	74.1	**0.03**	
Overweight	35	22.2		
Obese	25	3.7		
Waist circumference	73.5 (11.7)	67.9 (10.1)	0.088	**0.028**
Waist circumference percentile (%)				
<25th percentile	5	11.1	0.015	
25th to 75th percentile	20	59.3		
75th to 90th percentile	50	14.8		
>90th percentile	25	14.8		
Waist-to-height ratio, median (IQR)	0.510 (0.40;0.64)	0.460 (0.40;0.58)	**0.019**	**0.014**
WC/height ratio categories (%)				
Normal	45	77.8	**0.05**	
Intermediate	25	14.8		
High	30	7.4		
Metabolic syndrome (%)	25	3.7	0.07	
WC ≥75th percentile (%)	75	29.6	**0.002**	
SBP/DBP>90th percentile (%)	30	3.7	**0.032**	
Triglycerides ≥100 mg/dL (%)	10	7.4	1	
HDL-C <50 mg/dL (%)	40	37	1	
Fasting glucose ≥110 mg/dL (%)	0	0	-	
Cardiovascular risk factors (%)				
Hypertension	10	3.7	0.567	
Dyslipidemia	15	7.4	0.68	
Diabetes	0	0	-	
Insulin Resistance	5	11.1	0.6	

Table 1. (*Continued*)

	Psoriasis	Controls	*P* value	*P* value*
Excess adiposity				
1) BMI (%)				
Normal weight	40	74.1	**0.011**	
Overweight and obese	60	25.9		
2) WC percentile (%)				
<75th percentile	25	70.4	**0.003**	
>75th percentile	75	29.6		
3) Waist-to-height ratio (%)				
<0.490	45	77.8	**0.021**	
≥0.490	55	22.2		
Glucose, mean (SD), mg/dL	82.1 (4.4)	79.9 (6.8)	0.191	0.230
HbA1c, mean (SD), mg/dL	5.18 (0.18)	5.19 (0.23)	0.903	0.915
Triglycerides, median (IQR), mg/dL	48 (32; 229)	53 (27; 151)	0.796	0.750
Total cholesterol, mean (SD), mg/dL	160.6 (31.7)	157.7 (31.7)	0.759	0.763
LDL-C, mean (SD), mg/dL	94.1 (23.7)	90.8 (30.9)	0.690	0.690
HDL-C, mean (SD), mg/dL	53.8 (9.9)	54.9 (17.0)	0.786	0.796
VLDL-C, median (IQR), mg/dL	10.0 (8.0; 8.7)	11.0 (8.0; 15.0)	0.681	0.769
Ox-LDL, mean (SD), mg/dL	128.5 (45.2)	110.3 (31.8)	0.113	0.121
ApoB, mean (SD), mg/dL	65.6 (17.1)	60.5 (12.8)	0.247	0.260
Lp(a), mean (SD), mg/dL	34.7 (35.8)	26.6 (22.5)	0.344	0.359
hs-CRP, median (IQR), mg/L	0.54 (0.15; 2.97)	0.49 (0.15; 13.6)	0.561	0.363
HOMA, mean (SD)	1.99 (1.20)	1.84 (1.10)	0.641	0.610
Lipid profile				
All patients				
Ox-LDL, mean (SD), mg/dL	128.5 (45.2)	110.3 (31.8)	0.113	0.120
ApoB, mean (SD), mg/dL	65.6 (17.3)	60.4 (12.8)	0.247	0.255
BMI <85th percentile				
Ox-LDL, mean (SD), mg/dL	136.6 (47.3)	104.8 (28.4)	**0.037**	**0.035**
ApoB, mean (SD), mg/dL	70.6 (14.4)	59.1 (12.9)	**0.049**	**0.037**
BMI <85th percentile + WC <75th percentile + waist-to-height ratio ≤0.490				
Ox-LDL, mean (SD), mg/dL	147.8 (41.8)	107.0 (26.2)	**0.010**	**0.011**
ApoB, mean (SD), mg/dL	74.0 (12.7)	59.7 (11.74)	**0.019**	**0.018**

** Sex and age adjusted*

were obese compared to controls, this difference was not statistically significant, however there was an underlying trend toward obesity in psoriatic children, with an age- and sex-adjusted OR of 9.4 (95% CI 1.0-90.4).

Concerning central/visceral adiposity evaluation, using WC percentile and waist-to-height ratio, the age- and sex-adjusted odds of a WC percentile greater than 75 were significantly higher for children with psoriasis *vs* controls (OR 7.4; 95% CI 2.0-27.7), as the percentage of children with a WC percentile greater than 75 was significantly higher in psoriatic children than in controls (75% *vs* 29.6%, *P* = 0.002). However for a WC percentile greater than 90 (*vs* <90th percentile), there was no statistically significant difference (25% *vs* 14.8, *P*=0.380; OR 2.1; 95% CI 0.5-9.4). Waist-to-height ratio was significantly higher in children with psoriasis than controls (median (IQR): 0.510 (0.40; 0.64) *vs* 0.460 (0.40; 0.58), *P* = 0.019). A significantly higher percentage of children with psoriasis had a waist-to-height ratio above the normal range (>0.490) (55% *vs* 22.2%, *P*=0.021) with a 4.3-fold higher risk for excess central adiposity comparing to controls (OR 4.6; 95% CI 1.3-17.0). Finally, the OR of a waist-to-weight ratio ≥0.539 (*vs* <0.539) was 5.5 (95% CI 1.0-31.1), as 30% of psoriatic children *vs* 7.4% of controls (*P* = 0.05) had a waist-to-weight ≥0.539, *table 2*.

There was no difference in the other cardiovascular risk factors (hypertension, hypercholesterolemia, hypertriglyceridemia and diabetes) or insulin resistance. Concerning the lipid profile, no statistically significant difference was noted between the two groups. However, ox-LDL and apoB levels were higher in the psoriasis group (ox-LDL: 125.5 ± 45.2 mg/dL *vs* 110.3 ± 31.8mg/dL, *P* = 0.113 and apoB: 65.6 ± 17.3 mg/dL *vs* 60.4 ± 12.8 mg/dL, *P* = 0.247). Analysing exclusively patients without excess adiposity, considering only BMI <85th percentile or all three surrogate measures of excess adiposity (BMI <85th percentile

Table 2. Age- and sex-adjusted ORs

		OR (95% CI)		
Predicting	**Referent Control**	**BMI**	**WC**	**Waist-to-Height ratio**
Excess adiposity (overweight + obesity)	Normal weight	4.4 (1.2-15.6)	7.4 (2.0-27.7)	4.6 (1.3-17.0)
Obesity	Normal weight	13.4 (1.3-137.1)	5.0 (0.9-27.3)	7.5 (1.2-45.9)
Obesity	Overweight	4.6 (0.4-52.6)	0.5 (0.1-3.2)	2.4 (0.3-19.0)
Obesity	Overweight + normal weight)	9.4 (1.0-90.4)	2.1 (0.5-9.4)	5.5 (1.0-31.3)

+ WC <75th percentile + waist-to-height ratio ≤0.490), a statistically significant difference between psoriatic children and controls was found for ox-LDL (136.6 ± 47.3 *vs* 104.8 ± 28.4, p = 0.037; 147.8 ± 41.8 *vs* 107.0 ± 26.2, *P* = 0.010) and apoB (70.6 ± 14.4 *vs* 59.1 ± 12.9, *P* = 0.049; 74.0 ± 12.7 *vs* 59.7 ± 11.74, *P* = 0.019), with both groups maintaining no differences for age and sex.

The prevalence of metabolic syndrome was higher in the psoriatic group (25% *vs* 3.7%; *P* = 0.07), and although this difference was not statistically significant, there was an underlying trend toward an increased prevalence of metabolic syndrome in psoriatic children, with 2 components of the metabolic syndrome being significantly higher in the psoriasis group: waist circumference (75% *vs* 29.6%; *P* = 0.002) and SBP/DBP>90th percentile for age, gender and height (30% *vs* 3.7% *P* = 0.032).

Discussion

In this study, it was observed that children with psoriasis had a significantly greater prevalence and greater odds of excess adiposity and central adiposity than controls using several surrogate markers, such as BMI (≥85th percentile – OR 4.4; 1.2-15.6), WC (>75th percentile – OR 7.4; 2.0-27.7) and waist-to-height ratio (>0.490 – OR 4.6; 1.3-17.0). Moreover, a greater prevalence of metabolic syndrome was observed in children with psoriasis and although this difference was not statistically significant, there was an underlying trend toward an increased prevalence of metabolic syndrome in these patients comparing to controls (25% *vs* 3.7%; *P* = 0.07). Additionally, two components of the metabolic syndrome were significantly higher in the psoriasis group: waist circumference (75% *vs* 29.6%; *P* = 0.002) and the high blood pressure component (30% *vs* 3.7% *P* = 0.032). Finally, an altered and more atherogenic lipid profile was observed among psoriatic patients without excess adiposity.

It is well known that obesity and mainly central adiposity during childhood is associated with an increased risk of cardiovascular risk factors and cardiovascular disease and mortality in adulthood [25]. Current literature supports an association between psoriasis and obesity. A recent meta-analysis of cross-sectional and case-control studies showed that adult psoriasis patients have >50% increased odds of being obese, and that these odds are significantly higher for those with moderate-to-severe psoriasis than for patients with mild disease [26].

Although there is less data considering childhood psoriasis, some studies have addressed the association between excess adiposity and psoriasis in children and it has been observed that psoriatic children have a significantly greater risk of being overweight or obese and having increased central adiposity [8, 9, 14, 15]. Moreover, childhood psoriasis severity has been shown to be associated and/or influenced by excess adiposity, as, in a multi-centre, cross-sectional study of 409 psoriatic children, the odds ratio (95% CI) of obesity in psoriatic children *vs* controls was higher with severe psoriasis than mild psoriasis (4.92; 2.20-10.99 *vs* 3.60; 1.56-8.30) [8]. Interestingly, it has also been shown that overweight or obese children have increased odds of having psoriasis, as in an US cross-sectional study, overweight, moderately obese and extremely obese children had 1.31-, 1.39-, and 1.78-fold greater odds, respectively, of having psoriasis [16].

The precise mechanism underlying this association is unknown but it is probably multifactorial. Genetic and immune mediated mechanisms and behavioural factors such as diminished physical activity probably have an important role in explaining the association between psoriasis and obesity. The recent understanding of obesity as a pro-inflammatory state and adipose tissue, especially visceral adipose tissue, as an immune and endocrine organ, help explain the association between these two conditions [27]. In fact, overproduction of types 1 and 17 helper T-cell inflammatory cytokines has been associated with both obesity and psoriasis, which suggests that chronic inflammation may drive both conditions [28].

Adipocytes and inflammatory-type macrophages are key cell types that perpetuate inflammation within adipose tissue. Activated macrophages stimulate adipocytes to secrete inflammatory mediators, known as adipokines, such as leptin and resistin, that have been shown to be increased in psoriasis patients, which may promote activation of T cells and monocytes, driving both Th1 and Th17 immune responses and at the same time impairing the function of regulatory T cells [29]. Interestingly, low levels of regulatory adipokines have also been observed in psoriasis [30].

It is unclear if obesity precedes psoriasis or vice-versa. On the one hand, a prospective cohort study including 892 psoriatic women showed that increased adiposity preceded the onset of psoriasis [31], however, the pro-inflammatory state associated with psoriasis could be responsible and act as a driving force for the development of obesity and other cardiovascular comorbidities.

However, obesity-related inflammatory processes are probably more important, contributing to the severity of psoriasis rather than to the development the disease, since remission/amelioration of psoriasis has been reported after the treatment of obesity or bariatric surgery [32].

Thus, obesity and psoriasis are related and influence each other, probably deriving from a common underlying

pathophysiology. Common genetics may be in part responsible for the association between these two conditions, as this association is observed even at a young age.

Interestingly, higher levels of ox-LDL and apoB in psoriatic patients compared to controls were observed in this study, although without statistical significance. However, analysing exclusively patients without excess adiposity, a significant difference was found in the levels of ox-LDL and apoB in psoriatic children, two important players in the atherosclerotic process.

Over the past decade, several studies have established that the oxidatively-modified form of LDL is more important than native LDL in atherogenesis, as it enhances endothelial activation and/or dysfunction, processes widely accepted to be the earliest events in atherosclerosis [33]. Additionally, ox-LDL is considered a useful marker for cardiovascular diseases, as the measurement of ox-LDL correlates with the presence of CV disease, indicating that ox-LDL is a potential prognostic marker for future CV events [34].

Likewise, subendothelial retention of apoB-containing lipoproteins is an essential initiating event in atherogenesis and high plasma levels of apoB is a risk factor for atherosclerosis, while low levels may provide protection [35]. Moreover, apoB predicts ischemic cardiovascular events in both genders, being better than LDL in this respect [36].

Naturally, the interpretation of these results is limited by the small number of patients, although the observation of a more atherogenic lipid prolife among psoriatic children, independent of excess adiposity, should not be unnoticed. Moreover, Mallbris *et al* evaluated the plasma lipid, lipoprotein and apolipoprotein profiles in adult patients with onset of psoriasis within the past 12 months, comparing it with a closely matched control group and found that psoriatic patients had an aberrant lipoprotein composition, showing that patients with psoriasis are predisposed to lipid abnormalities. These results support the idea that an abnormal lipid profile and possibly other psoriasis linked co-morbidities may be genetically determined rather than acquired [37]. Recognizing genetic markers that could predict which patients are at risk of developing psoriasis-linked cardiovascular comorbidities would facilitate screening strategies and earlier management, with important clinical implications [38].

Concerning metabolic syndrome, a combination of cardiovascular risk factors, including central obesity, hypertension, glucose intolerance and dyslipidemia, is widely accepted as an important predictor of cardiovascular disease and type 2 diabetes; several studies in adult populations have shown its association with psoriasis [39]. A recent study evaluated the potential relationship between age at the onset of psoriasis on the frequencies of cardiovascular and metabolic comorbidities in adulthood and it was showed that childhood onset of psoriasis had no effect on the frequencies of metabolic and cardiovascular comorbidities, indicating that psoriasis duration does not appear to influence the development of cardiovascular/metabolic comorbidities [40].

Data on children, however, are scant. Au *et al* compared 20 children with psoriasis with a control group of 1563 aged matched from the NHANES database and showed a higher prevalence of metabolic syndrome in the psoriasis group (30% *vs* 7.4%: $P = 0.045$), although there was no statistically significant difference in body mass index or for any of the individual components of metabolic syndrome. Only the levels of HDL-C were found to be decreased in psoriasis patients (44.3 mg/dL *vs* 51.6 mg/dL, $P = 0.017$) [10].

Some limitations of this study should be addressed, particularly its sample size, therefore results must be interpreted with caution. Even so, in accordance with other previous studies, statistically significant differences were found between the two groups in several surrogate markers of obesity, mainly indicators for central obesity and metabolic risks (BMI, waist circumference and waist to height ratio). Moreover, although no statistically significant difference was found between psoriasis children and controls for the prevalence of metabolic syndrome, there was a trend towards an increased prevalence in the psoriasis group, with statistically significant differences in two metabolic syndrome components. Another limitation is the potential risk for selection bias, as in any hospital-based study design.

Amongst the strengths of this study are the validity of the diagnosis of cases and controls, made by the same dermatologist, the recruitment of children with similar psoriasis severity, the uniform data collection ensuring comparability of data collection in cases and controls and the use of several surrogate measures of excess adiposity, like BMI percentile, WC percentile and waist-to-height ratio. These last two, sensitive, non-invasive markers of central adiposity are superior indicators to BMI for metabolic risk, correlating better with a higher risk of cardiovascular risk factors, such as hypertension, hypercholesterolemia, hypertriglyceridemia and insulin resistance. Moreover, an extensive laboratory workup was performed, analysing the lipid profile and insulin resistance.

In conclusion, this study demonstrates that comorbidities known to be associated with adult psoriasis are also observed in childhood psoriasis. Moreover, an altered and more atherogenic lipid profile was observed among psoriatic patients without excess adiposity. The increased rate of cardiovascular comorbidities, particularly obesity and metabolic syndrome, observed in childhood psoriasis, along with the observation of lipid abnormalities at the onset of skin disease, suggests that its association with psoriasis may be in part genetically determined rather than uniquely acquired. These results reinforce the need for screening for cardiovascular comorbidities in children with psoriasis, mainly obesity and central adiposity, and to promote healthy lifestyle choices in these young patients. ■

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Influência de Polimorfismos Genéticos na IL-6 na Gordura Epicárdica e Calcificação Arterial Coronária em Doentes com Psoríase

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Influence of IL-6 gene polymorphisms in epicardial adipose tissue and coronary artery calcification in psoriasis patients

Short title: IL-6 gene polymorphisms and epicardial adipose tissue in psoriasis

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Psoriasis is currently considered a systemic inflammatory disorder associated with several comorbidities and increased risk of cardiovascular disease (CVD)[1]. Several proinflammatory cytokines are overexpressed cutaneous and systemically and may be responsible for skin lesions but also for psoriasis-associated conditions[1]. Epicardial adipose tissue (EAT), a type of visceral fat surrounding the heart, is now regarded as an important factor in the pathogenesis of coronary atherosclerosis and CVD, through inflammatory burden proximal to the coronary arteries, and has been shown to be increased in psoriasis patients independently of abdominal visceral fat (AVF) and to be associated with subclinical atherosclerosis[2].

IL-6 has been implicated in the pathogenesis of psoriasis[1] but also of abdominal obesity[3], atherosclerosis and CVD[4]. IL-6 is produced by several cells, with adipose tissue accounting for up to 30% of total circulating concentrations in healthy subjects[3]. The expression of many cytokines is thought to be influenced by polymorphisms in their gene loci, and this may contribute to the development of psoriasis, but also excess adiposity[3]. The association between IL-6 polymorphisms and psoriasis has been investigated[5], as well as, with excess adiposity[3]. Recognizing genetic markers that could predict which patients are at risk of developing psoriasis-linked cardiovascular comorbidities may permit an earlier management, with important clinical implications[6]. This study aimed to evaluate the potential contribution of four IL-6 genetic variants (rs1800795[-174G>C], rs1800796[-572G>C], rs2069827[-1426G>T], rs2069840[-1753C>G]) in psoriasis susceptibility and its influence in EAT and coronary artery calcification (CAC) in severe psoriasis patients.

Consecutive Portuguese, European ancestry, adult patients with severe plaque-type psoriasis (PASI>10 and/or requiring systemic therapy/phototherapy) without psoriatic arthritis, CVD, and other systemic inflammatory disease were enrolled. All subjects underwent clinical and laboratory evaluation, DNA sample extraction and multidetector computed tomography scan for EAT, AVF and CAC assessment. The scan parameters and used methods have been previously described[2]. The Control DNA group was obtained from a previously anonymized DNA biobank of 206 adult Portuguese general population controls without psoriasis. SNP genotyping was performed on the Sequenom™massARRAY iPLEX platform. The study was approved by the hospital Institutional Review Board.

No significant differences were observed in genotype or allele frequencies between psoriasis patients and controls (table 1). Psoriasis patients homozygous for the minor G-allele of the rs2069840 polymorphism had increased EAT volume comparing to those carrying the C-allele (CC+CG) (136.05±87.20vs95.32±45.98,P=0.008) independently of age, sex and AVF(P=0.031). Analysing allele distribution, G-allele presence was associated with increased EAT volume, comparing to C-allele, independently of age, sex and AVF (110.39±65.77vs95.33±46.33, adjusted P=0.026). No significant differences were found when analysing other polymorphisms. None of the polymorphisms showed a significant association with the presence of CAC, both in the unadjusted analysis and after adjusting for age, sex and traditional CVRF(table 2).

The present study showed that psoriasis patients carrying the minor G-allele of the IL-6 rs2069840 polymorphism had increased EAT volume independently of age, sex and AVF. This effect appeared to be enhanced in the homozygous status for the G-allele. However, none of the studied SNPs was associated with increased risk of CAC. Atherosclerosis is a polygenic disease and a single gene variable may not be enough to explain the development of atherosclerotic disease. Finally, no differences were observed in genotype or allele frequencies between psoriasis patients and controls.

Probably there are other factors and inflammatory pathways, rather than genetic contribution, which mainly define IL-6 levels in psoriasis patients.

More than one polymorphic site in the IL-6 gene has been suggested to influence gene transcription, both in the promoter or intron region. The rs1800795 variant is the best-studied IL-6 polymorphism, but data on its effects in psoriasis, excess adiposity and IL-6 expression has been inconsistent[5,7,8]. IL-6 rs2069827 polymorphism has been associated with adiposity[8] while rs2069840 variant has not yet been associated with any chronic inflammatory disease or excess adiposity, but has been associated both with higher and reduced IL-6 plasma levels[9]. Possibly the effect of the IL-6 polymorphisms on IL-6 expression and the effect of IL-6 itself may vary by situation or cell type[7,8].

The way IL-6 polymorphism influences EAT or overall adiposity is unknown, but some IL-6 genotypes may be associated with lower fasting energy expenditure providing a hypothesis for some polymorphism to influence long-term weight gain and obesity[10].

Some limitations should be addressed: the cross-sectional method of the study prevents proving causality, serving solely for hypothesis-generation; the relatively small studied population; a haplotype analysis could provide further insight than the effects of single SNPs; although, the measurement of circulating IL-6 levels may not reflect biological significance at tissue level, serum IL-6 levels were not measured, making it impossible to conclude on the functional consequences of the IL-6 polymorphisms on the excess adiposity observed.

Although further studies in other psoriasis populations are warranted, genetic variants in the IL-6 gene may have a role in the association between psoriasis and its comorbidities and be involved in the development of increased EAT in these patients.

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Table 1 Genotype and allele frequencies for IL-6 gene polymorphisms in psoriasis and control subjects

	Psoriasis 100 % (n)	Controls 206 % (n)	P [#]	OR (95% CI) [*]
rs2069840				
CC	34% (34)	40.8% (84)		1
CG	51% (51)	47.6% (98)		1.63 (0.90-2.93)
GG	15% (15)	11.7% (24)	0.459	1.22 (0.52-2.86)
C	59.5% (119)	64.6% (266)		1
G	40.5% (81)	35.4% (146)	0.224	1.21 (0.82-1.73)
rs1800795				
GG	42% (42)	35.0% (72)		1
GC	45% (45)	53.4% (110)		0.83 (0.47-1.47)
CC	13% (13)	11.7% (24)	0.380	1.13 (0.48-2.66)
G	64.5% (129)	61.7% (254)		1
C	35.5% (71)	38.4% (158)	0.494	0.99 (0.67-1.46)
rs1800796				
GG	90% (90)	85.4% (176)		1
GC	8% (8)	13.6% (28)		0.64 (0.26-1.57)
CC	2% (2)	1% (2)	0.264	1.79 (0.23-13.88)
G	94% (188)	92.2% (380)		1
C	6% (12)	7.8% (32)	0.427	0.85 (0.41-1.77)
rs2069827				
GG	83% (83)	83.5% (172)		
GT	17% (17)	16.5 (34)		
TT	0% (0)	0% (0)	N/A	N/A
G	91.5% (183)	91.7% (378)		1
T	8.5% (17)	8.3% (34)	0.917	1.00 (0.51-1.99)

[#] Unadjusted P

* Age- and sex-adjusted odds ratio

N/A – test not performed – no patients with TT genotype

Table 2 - Influence of the IL-6 polymorphisms in EAT volume and coronary artery calcification

	EAT	P #	P *		CAC=0	CAC>0	P #	OR (95% CI) +
rs2069840								
CC (34)	95.36±47.91				28.1% (16)	41.9% (18)		1
GC (51)	95.29±45.13				61.4% (35)	37.2% (16)		0.41 (0.06-2.92)
GG (15)	136.05±87.20	**0.031**	0.060		10.5% (6)	20.9% (9)	0.051	0.85 (0.21-3.23)
CC+CG (85)	95.32±45.98				89.5% (51)	79.1% (34)		1
GG (15)	136.05±87.20	**0.008**	**0.031**		10.5% (6)	20.9% (9)	0.149	2.23 (0.36-13.85)
C (119)	95.33±46.33				58.8% (67)	60.5% (52)		1
G (81)	110.39±65.77	0.059	**0.026**		41.2% (47)	39.5% (34)	0.809	0.73 (0.31-1.70)
rs1800795								
GG (42)	112.80±63.08				40.4% (23)	44.2% (19)		1
GC (45)	96.67±49.69				47.4% (27)	41.9% (18)		2.06 (0.55-7.73)
CC (13)	81.16±42.46	0.148	0.529		12.3% (7)	14.0% (6)	0.859	1.83 (0.26-13.06)
G (129)	107.18±58.80				64.0% (73)	65.1% (56)		1
C (71)	90.99±47.18	**0.048**	0.313		36.0% (41)	34.9% (30)	0.874	1.47 (0.63-3.43)
rs1800796								
GG (90)	102.54±56.73				87.7% (50)	93% (40)		
GC (8)	96.89±48.34				8.8% (5)	7% (3)		
CC (2)	69.50±10.60	0.691	0.854		3.5% (2)	0% (0)	N/A+	N/A+
G (188)	102.30±56.14				92.1% (105)	96.5% (83)		1
C (12)	87.76±41.10	0.379	0.748		7.9% (9)	3.5% (3)	0.194	0.38 (0.04-3.70)
rs2069827								
GG (83)	103.18±56.23				80.7% (46)	86% (37)		
GT (17)	92.88±53.80				19.3% (11)	14% (6)		
TT (0)	…	N/A#	N/A#		…	…	N/A+	N/A+
G (183)	102.22±55.60				90.4% (103)	93.0%(80)		1
T (17)	92.88±53.80	0.507	0.686		9.6% (11)	7.0% (6)	0.502	1.06 (0.25-4.41)

Unadjusted P

* Age-, sex- and AVF-adjusted P

+ OR (95% CI) Age-, sex- and traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, tabaco use, obesity and family history of coronary heart disease)-adjusted odds ratio

N/A# – test not performed – no patients with TT genotype

N/A+ – test not performed – no patients in CC genotype/CAC>0 group; no patients with TT genotype

EAT – epicardial adipose tissue; CAC – coronary artery calcification

Influência de Polimorfismos Genéticos na TNF-α na Calcificação Arterial Coronária em Doentes com Psoríase

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Influence of TNF-α gene polymorphisms in coronary artery calcification in psoriasis patients

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Influence of TNF-α gene polymorphisms in coronary artery calcification in psoriasis patients

TNF-α gene polymorphisms and coronary artery calcification in psoriasis patients

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Psoriasis is a systemic inflammatory disorder associated with numerous medical comorbidities and increased risk of cardiovascular disease (CVD)[1]. Psoriasis' systemic inflammation may play an important role in the accelerated atherosclerosis observed in these patients[2] as inflammatory processes play a key role in atherogenesis[3]. Psoriasis and atherosclerosis share some pathological features including endothelial dysfunction, alteration in angiogenesis, and some inflammatory pathways[2]. TNF-α is a potent pro-inflammatory cytokine that has been implicated in psoriasis and atherosclerosis pathogenesis[2,4] and its synthesis is tightly regulated at gene transcription level[5]. TNF-α gene promoter region contains several single nucleotide polymorphisms (SNP) that influence TNF-α production[6]. Several TNF-α gene polymorphisms have been associated with psoriasis and CVD[7-9]. A recent meta-analysis suggested that TNF-α rs1800629(308G/A) polymorphism was associated with decreased risk of psoriasis, while TNF-α rs361525(238G/A) was associated with increased risk[7]. Regarding TNF-α rs1799964 (1031T/C) polymorphism, existing data is limited and contradictory[8]. Since psoriasis morbidity and mortality are strongly linked to accelerated atherosclerosis, determining the genetic contribution for cardiovascular morbidity in psoriasis patients becomes an issue of major importance. The aim of this study was to evaluate the contribution of TNF-α rs361525(238G/A), TNF-α rs1800629(308G/A) and TNF-α rs1799964(1031T/C) gene polymorphisms to coronary artery calcification (CAC) in severe psoriasis patients.

Consecutive patients with severe plaque-type psoriasis observed at our Department were enrolled. Exclusion criteria included the presence of psoriatic arthritis, CVD (as previously defined[10]) and other systemic inflammatory diseases. All subjects underwent clinical and laboratory evaluation, DNA sample extraction and multidetector computed tomography scan for CAC assessment (scan parameters previously described[10]). Control DNA group was obtained from a previously anonymised biobank of 206 healthy individuals. SNP genotyping was performed using Sequenom™ massARRAY-iPLEX platform. The study was approved by the hospital Institutional Review Board.

One hundred psoriasis patients were enrolled(table1). None of the studied polymorphisms showed a significant association with the presence of CAC, both in the unadjusted analysis and after adjusting for age, sex and traditional cardiovascular risk

factors (CVRF)(Table2). Similarly, none of the studied polymorphisms showed a significant association with patients' clinical and analytic characteristics (psoriasis characteristics, lipid profile, insulin resistance and inflammation biomarkers), both in the unadjusted analysis and after adjusting for age and sex(data not shown). No significant differences were observed in the genotype or allele frequencies between patients and controls(table2).

This is the first study to specifically evaluate the influence of TNF-α gene polymorphisms in the development of subclinical atherosclerosis in patients with psoriasis. No significant association was found between the studied polymorphisms and the presence of CAC.

The systemic inflammatory status present in psoriasis may act as an atherosclerotic independent risk factor[1]. TNF-α has a deleterious effect over endothelial cells, promoting endothelial dysfunction through impairment of nitric oxide bioavailability and endothelial repair and endothelial injury through recruitment of immune cells that mediate tissue destruction[3,4]. Recognizing genetic markers that could predict which patients are at risk of developing CVD would permit an earlier management, ease screening strategies, leading to early, aggressive CVRF management. The association between TNF-α gene polymorphisms and CVD[9] has been evaluated, however results have been inconclusive[9]. Serum TNF-α levels are affected by multiple environmental and genetic factors[7,9]. Thus, it is possible that some additional factors may be required to promote development of atherosclerosis mediated by the TNF-α variant in patients with psoriasis.

Strengths of this study include the homogenous patient sample and the detailed clinical, laboratory and imaging characterization of all psoriasis patients, as CAC assessment is a very sensitive and specific non-invasive measure of subclinical atherosclerosis. The main limitations are the low number of patients analysed, the cross-sectional observational method and the lack of TNF-α serum measurement, making it impossible to conclude on the functional consequences of TNF-α polymorphisms.

In conclusion, at least in this cohort of patients, these three TNF-α gene polymorphisms do not appear to be associated with CAC. The search for potential

genes that may influence the development of atherosclerosis in psoriasis patients is warranted.

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Table 1 – Study population characteristics

	N=100
Gender, male	64%
Age, y	47.4±10.87
Metabolic characteristics	
Body mass index, kg/m2	28.6±4.99
Waist circumference, cm	95.8±12.16
Systolic blood pressure, mmHg	133.6±16.14
Diastolic blood pressure, mmHg	80.9±8.87
Cardiovascular risk factors	
Hypertension	49%
Diabetes	12%
Dislipidemia	43%
Tabaco use	21%
Obesity	37%
Family history of cardiovascular disease	13%
Metabolic Syndrome	32%
Psoriasis characteristics	
Psoriasis duration	21.9±10.97
Family history	43%
PASI	13.4±7.67
Psoriasis therapy*	
Topical only	16%
Ever phototherapy	61%
Ever acitretin	30%
Ever cyclosporine	51%
Ever methotrexate	33%
Ever biologic therapy	21%
Analytic characteristics	
Total cholesterol, mg/dl	206.5±39.9
Triglycerides, mg/dl	107 (71.3-155)
HDL-cholesterol, mg/dl	51.5±13.2
LDL-cholesterol, mg/dl	129.1±38.2
Oxidized LDL-cholesterol, mg/dl	183.4±56.4
Apolipoprotein B, mg/dl	94.0±24.3
Lipoprotein(a), mg/dl	22.5 (6-46.8)
Complement C3, mg/dl	127.2±20.5
C-reactive protein, mg/dl	2.4 (1.0-4.7)
HOMA	2.2 (1.4-3.5)
Atherosclerosis assessment	
Presence of atherosclerosis (CAC>0)	43%

Mean±standard deviation; Median (interquartile range)

HOMA - homeostatic model assessment

Table 2 – Influence of TNF-α polymorphism in coronary artery calcification and psoriasis susceptibility

Influence of TNF-α polymorphism in coronary artery calcification				
	CAC=0	CAC>0	P #	OR (95% CI) *
rs361525 (-238G/A)				
GG	87.7% (50)	86.0% (37)		
GA	12.3% (7)	14.0% (6)		
AA	0% (0)	0% (0)	N/A	N/A
G	93.9% (107)	93.0% (80)		1
A	6.1% (7)	7.0% (6)	0.812	1.70 (0.36-8.13)
rs1800629 (308G/A)				
GG	80.7% (46)	65.1% (28)		1
GA	15.8% (9)	32.6% (14)		2.24 (0.56-8.94)
AA	3.5% (2)	2.3% (1)	0.141	1.41 (0.050-39.40)
G	88.6% (101)	82.6% (71)		1
A	11.4% (13)	17.4% (15)	0.223	1.54 (0.51-4.71
rs1799964 (1031T/C)				
TT	68.4% (39)	55.8% (24)		1
TC	29.8% (17)	41.9% (18)		2.59 (0.68-9.90)
CC	1.8% (1)	2.3% (1)	0.433	0.42 (0.01-200.10)
T	83.3% (95)	76.7% (66)		1
C	16.7% (19)	23.3% (20)	0.244	1.89 (0.61-5.89)
TNF-α gene polymorphisms genotype and allele frequencies				
	Psoriasis (n=100)	Controls (n=206)	P #	OR (95% CI) +
rs361525 (-238G/A)				
GG	87.0% (87)	91.3% (188)		
GA	13.0% (13)	8.7% (18)		
AA	0% (0)	0% (0)	N/A	N/A
G	93.5% (187)	95.6% (394)		1
A	6.5% (13)	4.4% (18)	0.325	1.57 (0.69-3.57)
rs1800629 (308G/A)				
GG	75.0% (75)	77.2% (159)		1
GA	23.0% (23)	21.8% (45)		1.07 (0.54-1.93)
AA	2.0% (2)	1.0% (2)	0.751	3.08 (0.37-25.47)
G	86.5% (173)	88.1% (363)		1
A	13.5% (27)	11.9% (49)	0.602	1.15 (0.66-2.02)
rs1799964 (1031T/C)				
TT	59.0% (59)	50.5% (104)		1
TC	35% (35)	40.3% (83)		0.73 (0.41-1.29)
CC	6% (6)	9.2% (19)	0.323	0.39 (0.13-1.16)
T	76.5% (153)	70.7% (290)		1
C	23.5% (47)	29.3% (120)	0.134	0.66 (0.43-1.028)

[#] Unadjusted P

[*] OR (95% CI) Age-, sex- and traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, tabaco use, obesity and family history of coronary heart disease)-adjusted odds ratio

[+] Age- and sex-adjusted odds ratio

N/A – test not performed – no patients with AA genotype

Influência de Polimorfismos Genéticos da Leptina, Receptor de Leptina e Adiponectina na Gordura Epicárdica, Gordura Visceral Abdominal e Calcificação Arterial Coronária em Doentes com Psoríase

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Torres T, Bettencourt N, Ferreira J, Carvalho C, Mendonça D, Pinho-Costa P, Vasconcelos C, Selores M, Silva B.
Lack of association between leptin, leptin receptor and adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat and atherosclerotic burden in psoriasis patients. (submetido)

Title: Lack of association between leptin, leptin receptor and adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat and atherosclerotic burden in psoriasis patients

Short title: Leptin, leptin receptor and adiponectin gene polymorphisms and excess adiposity and atherosclerotic burden in psoriasis patients

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Abstract

Background:Identifying psoriasis patients who present a higher risk of developing cardiovascular comorbidities is of upmost importance. Recognizing genetic markers that could predict which patients are at higher risk may permit an earlier management, with important clinical implications. Two key adipokines, leptin and adiponectin, may play a role connecting psoriasis and its major comorbidities.

Objectives:To evaluate the potential contribution of LEPrs2167270(19G/A), LEPRrs1137100(326A/G) and ADIPOQrs1501299(276G/T) gene polymorphisms in psoriasis susceptibility and their influence in epicardial adipose tissue and abdominal visceral fat volume and subclinical atherosclerosis in severe psoriasis patients

Materials&Methods:100 severe psoriasis patients underwent clinical and laboratory evaluation, DNA genotyping and multidetector computed tomography scan for epicardial adipose tissue, abdominal visceral fat and coronary artery calcification assessment. DNA control group was obtained from a previously anonymized biobank of 206 adult subjects without psoriasis.

Results:No significant difference was found between the studied polymorphism and epicardial adipose tissue and abdominal visceral fat volume. None of the polymorphisms showed a significant association with the presence of subclinical atherosclerosis, both in the unadjusted analysis and after adjusting for age, sex and cardiovascular risk factors. No significant differences were observed in the genotype or allele frequencies between patients and controls.

Conclusion:The studied polymorphisms does not seem, at least in this cohort of patients, to be a genetic risk factor for the development of atherosclerosis or increased adiposity in psoriasis, neither for psoriasis susceptibility. The search for potential gene candidates that may influence the development of atherosclerosis and psoriasis-linked comorbidities in patients with psoriasis needs further investigation.

Key words: Leptin, leptin receptor, adiponectin, gene polymorphism, psoriasis, epicardial adipose tissue, cardiovascular disease, atherosclerosis

Introduction

Leptin and adiponectin are two major adipocyte-secreted hormones with pleiotropic effects on metabolism, inflammation and insulin resistance being central factors underlying metabolic disorders[1,2]. Genetic variants in genes encoding these adipokines are known to contribute to variations in their plasma levels and to the development of several cardiometabolic conditions[3,4]. Polymorphisms in the leptin (LEP) and leptin receptor (LEPR) gene have been reported to be associated with obesity and higher leptin levels in obese individuals[5,6], while several adiponectin gene (ADIPOQ) single nucleotide polymorphisms (SNPs) have been shown to influence adiponectin levels and to be associated with a higher risk for obesity, cardiovascular disease and type-2 diabetes[3,7].

Psoriasis is a systemic inflammatory disorder associated with several cardiometabolic comorbidities and with clinically significant increased risk of cardiovascular disease (CVD) and cardiovascular mortality[8-11]. Also the increased inflammatory load of psoriasis may play an important role in the accelerated atherosclerosis observed in these patients[12]. Recently psoriasis has been associated with increased epicardial adipose tissue (EAT) and abdominal visceral fat (AVF)[13,14]. The mechanism linking psoriasis, its associated comorbidities and CVD has not yet been elucidated, but is probably related to common pathogenic mechanisms, shared genetic risk variants and environmental triggers or a combination of these factors[15].

Elevated leptin levels and leptin receptor expression have been reported to be associated with psoriasis and several studies have suggested leptin secretion to be positively correlated with body mass index and to possibly contribute to cardiovascular disease in psoriasis[1,16]. On the other hand, psoriasis has been associated with decreased plasma adiponectin levels independently of cardiometabolic risk factors[1,17].

Leptin gene polymorphisms and their association with psoriasis have not been extensively studied[18-21] and the results have been contradictory, while to date, no studies have evaluated LEPR and ADIPOQ gene polymorphism in psoriasis. The most studied Leptin gene polymorphism in psoriasis has been LEP (-2548G/A). One study has detected significant differences accompanied by varying levels of leptin[19], while two other studies found no statistically significant differences between patients and healthy controls[20,21]. Recently, another Leptin polymorphism (rs2060713) has been study in psoriasis and no statistically significant differences were observed between patients and controls[18].

The aim of this study was to evaluate the potential contribution of the LEP rs2167270 (19G/A), LEPR rs1137100 (326A/G) and ADIPOQ rs1501299 (276G/T) polymorphisms in psoriasis susceptibility and their influence in EAT, AVF and coronary artery calcification (CAC) in severe psoriasis patients.

Methods

Consecutive patients with severe plaque-type psoriasis (PASI > 10% and/or disease requiring systemic therapy or phototherapy) observed at our Psoriasis Center were enrolled. Exclusion criteria included the presence of psoriatic arthritis (previous/current signs/symptoms of joint evolvement), the presence of cardiovascular disease (as previously defined[13]) and the presence of other systemic inflammatory disease (lupus erythematous, rheumatoid arthritis or other spondyloarthropathies).

All subjects underwent clinical evaluation (complete medical history and physical examination), laboratory evaluation, DNA sample extraction and multidetector computed tomography (MDCT) scan for EAT, AVF and coronary artery calcification (CAC) assessment. MCDT scan parameters and used methods have been previously described[13] . The control DNA group was obtained from a previously anonymised DNA biobank of 206 local general population controls without psoriasis. SNP genotyping was performed on the Sequenom™ massARRAY iPLEX platform (Sequenom, San Diego, CA) using multiplexed amplification followed by mass-spectrometric product separation. The study was approved by the hospital Institutional Review Board and subject's written consent was obtained according to the declaration of Helsinki.

Statistical analysis

Variables were tested for normality using Kolmogorov-Smirnov test. Descriptive statistics are presented as percentage for categorical variables and mean±standard deviation or median with interquartile range according to the distribution of the continuous variables. Chi-squared test or Fisher's exact test were used, as appropriate, to test group differences of proportions.

Within psoriasis patients the association between genotypes and alleles of the studied polymorphisms and EAT and AVF volume was tested using analysis of covariance (ANCOVA) adjusting for gender, age and AVF and gender and age respectively. The association between the presence of subclinical atherosclerosis (CAC>0) and the studied polymorphisms was performed using multivariable logistic regression adjusted for confounders. The level of statistical significance was set at α=0.05. Statistical analyses were performed with SPSS version 21 (SPSS IBM, New York, U.S.A).

Results

A total of 100 psoriasis patients and 206 controls were enrolled. Genotype frequencies of the studied polymorphisms were in Hardy-Weinberg equilibrium in patients and controls and no

significant differences were observed in the genotype or allele frequencies between both groups, before and after adjustment for age and sex.

Concerning the influence of the LEP, LEPR and ADIPOQ polymorphisms in EAT and AFV volume, no significant differences was found. Similarly, none of the polymorphisms showed a significant association with the presence of CAC, both in the unadjusted analysis and after adjusting for age, sex and traditional cardiovascular risk factors (CVRF). Finally, when psoriasis patients were stratified according to clinical characteristics (metabolic and CVRF), analytic characteristics (lipid profile, insulin resistance, inflammation (hs-CRP)) and psoriasis clinical features (age at onset of the disease, psoriasis severity, family history), no significant differences, in the allele or genotype frequency of any the studied polymorphism were found after adjustment for age and sex. Also for leptin levels, no significant differences were found.

Discussion

In the present study, no association was observed between polymorphisms of leptin (LEP rs2167270 [19G/A]), leptin receptor (LEPR rs1137100 [326A/G]) and adiponectin (ADIPOQ rs1501299 [276G/T]) genes and psoriasis susceptibility, CAC or increased EAT or AVF volume. To the best of our knowledge, studies aimed to establish the potential influence of LEP, LEPR and ADIPOQ gene polymorphisms in the EAT and AVF volume and development of subclinical atherosclerosis in patients with psoriasis have not been reported.

It is well established that the expansion of visceral adipose tissue, currently regarded as an immune and endocrine organ, is associated with a higher risk for cardiometabolic comorbidities and cardiovascular disease, due to the release of several pro-inflammatory cytokines and adipokines[2,22]. AVF have been shown to be increased in psoriasis independently of waist circumference and may be a potential link between psoriasis and its metabolic comorbidities[14]. Also EAT, a type of visceral adipose tissue surrounding the heart and coronary vessels that produces several proatherosclerotic and proinflammatory hormones and cytokines, including IL-6, TNF-a, leptin, and MCP-1[23], has been shown to be increased in psoriasis patients and to be associated with subclinical atherosclerosis[13], probably through its metabolic effects both at a paracrine and systemic level[23,24].

Psoriasis is a complex polygenic disease and several genes have been implicated in both disease susceptibility and increased risk of CV mortality[25]. Recognizing genetic markers that could predict which patients are at risk of developing psoriasis-linked cardiovascular comorbidities may permit an earlier management and ease screening strategies, leading to early, aggressive risk factors management including patient education to adopt healthy life-style behaviours, such as, smoking cessation, weight control and exercise[26].

Leptin and adiponectin are adipokines that may possible connect psoriasis with its major comorbidities, as they have been shown to play a role in excess adiposity, development of cardiovascular disease and in psoriasis[1].

Leptin is predominantly synthesized and secreted by adipocytes, being implicated in the regulation of body weight by inhibiting food intake and stimulating energy expenditure and its action occurs through a leptin receptor[1,27]. Increased levels of leptin have been associated with cardiovascular disorders and to be an independent predictor of coronary heart disease[28]. Leptin also modulates both innate and adaptive immunity, playing a role in acute and chronic inflammation, via regulation of cytokine expression, acting as a modulator of T-cell activity[29]. Leptin plasma levels have been reported to be increased in psoriatic patients[1,30] and to be associated with higher PASI scores[31]. Leptin appears to contribute to Th1 and suppresses Th2 immune responses, increasing IL-2 secretion and proliferation, as well as increasing IFN-γ production by memory T cells, and inhibiting the proliferation of CD4+FoxP3+ T regulatory cells[32]. Leptin also increases macrophage activity and their production of IL-1β, IL-6, TNF-α and IL-12[32]. Thus, Leptin, through promoting synthesis of Th1 cytokines and diminished T regulatory activity may be involved in the pathogenesis of psoriasis[32,33].

The LEP rs2167270 (19G/A) polymorphism has never been studied before in psoriasis patients. It has been reported to be associated with obesity and higher leptin levels in obese individuals[4,34]. On the other hand, it has been shown that women carrying the A-allele had lower BMI and lower leptin levels than those not carrying this allele. Also variants in LEPR have also been associated with obesity[5]. LEPR rs1137100 (326A/G) have been shown to be associated with adiposity, although some studies, probably as a result of ethnic differences in allele frequencies, have not showed this association[6].

Regarding adiponectin, it is secreted mostly by adipocytes, exerting insulin sensitizing effects and anti-inflammatory and atheroprotective actions by reducing the expression of vascular adhesion molecules (VCAM-1), inflammatory cytokines (TNF-a and IL-8) and reactive oxygen species in endothelial cells[1,35]. Its levels have been found to be decreased in obesity, type 2 diabetes and coronary artery disease[36-38]. Several studies have reported decreased circulating levels of adiponectin in patients with psoriasis compared to a control group and that adiponectin concentration levels are negatively correlated with psoriasis severity[39,40]. Moreover, obese psoriasis patients appear to have decreased adiponectin serum levels. Adiponectin concentrations have a strong genetic component, with heritability estimated between 30% and 50%[3]. Polymorphisms located in the ADIPOQ gene exert high influence on adiponectin serum levels, and although there are conflicting results, the major allele G of the rs1501299 (276G/T) has been associated with cardiovascular disease[41], while the minor allele T

was associated with a reduced frequency of CV disease, possible due to different effect on adiponectin levels[42,43].

The chronic inflammatory status associated with psoriasis seems to be responsible for accelerated atherosclerosis and higher risk of CVD. Nevertheless, in the present study, none of the studied gene polymorphisms showed a significant association with coronary artery calcification. Atherosclerosis is a polygenic disease and a single gene variable may not be enough to explain the development of the atherosclerotic disease, since the subtle nature of the genetic effects of a single locus polymorphism are prone to be masked by confounding factors. Naturally, large-scale genetic screening is required to analyse the epigenetic effects of inflammatory genes on cardiovascular events and mortality in psoriasis patients.

Strengths of this study include the detailed clinical, laboratory and imaging characterization of all psoriasis patients. The imaging method used to assess EAT and AVF is, along with MRI, the gold standard to measure EAT, also enabling AVF quantification, the most reliable marker of excess adiposity. Additionally, a very sensitive and specific non-invasive measure of subclinical atherosclerosis was used. The homogenous patient sample is also a strength of the study, as all patients had severe psoriasis and psoriatic arthritis and known CVD were exclusion criteria. However, some limitations should be addressed. Despite being the largest study focusing on genetic variants of the LEP, LEPR and ADIPOQ genes and EAT, AVF and CAC in psoriasis, this is still a relatively small single centre study. Other limitation is the cross-sectional, observational method of the study, which prevents proving causality, serving solely for hypothesis-generation. Finally, only leptin serum levels were measured, although no significant differences were found regarding the genotype and allele frequencies.

In conclusion, the studied polymorphisms in the LEP, LEPR and ADIPOQ genes does not seem to be a genetic risk factor for the development of atherosclerosis or increased adiposity in psoriasis, neither for psoriasis susceptibility. Although studies with positive results are usually more appealing than those with negative findings[44,45], the results presented might be useful for further research. Due to the potential role of these adipokines in the pathophysiology of psoriasis, excess adiposity and cardiovascular disease, other polymorphisms located in these genes might have an influence in the development of atherosclerosis and excess adiposity in psoriasis. The search for potential gene candidates that may influence the development of atherosclerosis and psoriasis-linked comorbidities in patients with psoriasis needs further investigation.

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Table 1 – Study population characteristics

	N=100
Gender, male	64%
Age, y	47.4±10.87
Metabolic characteristics	
Body mass index, kg/m2	28.6±4.99
Waist circumference, cm	95.8±12.16
Systolic blood pressure, mmHg	133.6±16.14
Diastolic blood pressure, mmHg	80.9±8.87
Cardiovascular risk factors	
Hypertension	49%
Diabetes	12%
Dislipidemia	43%
Tabaco use	21%
Obesity	37%
Family history of CVD	13%
Metabolic Syndrome	32%
Psoriasis characteristics	
Psoriasis duration	21.9±10.97
Family history	43%
PASI	13.4±7.67
Psoriasis therapy*	
Topical only	16%
Ever phototherapy	61%
Ever acitretin	30%
Ever cyclosporine	51%
Ever methotrexate	33%
Ever biologic therapy	21%
Analytic characteristics	
Glucose, mg/dl	93.3±28.3
Total cholesterol, mg/dl	206.5±39.9
Triglycerides, mg/dl	107 (71.3-155)
HDL-cholesterol, mg/dl	51.5±13.2
LDL-cholesterol, mg/dl	129.1±38.2
VLDL-cholesterol, mg/dl	22.0 (14.0-32.5)
Oxidized LDL-cholesterol, mg/dl	183.4±56.4
Apolipoprotein B, mg/dl	94.0±24.3
Lipoprotein(a), mg/dl	22.5 (6-46.8)
Complement C3, mg/dl	127.2±20.5
hs-C-reactive protein, mg/dl	2.4 (1.0-4.7)
Leptin, mg/dl	0.7 (0.4-1.6)
HOMA	2.2 (1.4-3.5)
Adipose tissue assessment	
Epicardial Adipose fat tissue, ml	101.4±55.52
Abdominal visceral fat, ml	136.7±84.02

Subcutaneous fat, ml	242.1±108.85
Atherosclerosis assessment	
Presence of atherosclerosis (CAC>0)	43%

Mean±standard deviation; Median (interquartile range)
HOMA – homeostatic model assessment
CVD – cardiovascular disease

Table 2 – Genotype and allele frequencies for studied polymorphisms in psoriasis and control subjects

	Psoriasis (n=100)	Controls (n=206)	P [#]	OR (95% CI) [*]
LEP rs2167270 (19G/A)				
GG (n=39)	39.0% (39)	35.0% (72)		1
GA (n=50)	50.0% (50)	47.1% (97)		1.04 (0.58-1.86)
AA (n=11)	11.0% (11)	18.0% (37)	0.286	0.52 (0.22-1.23)
G (n=128)	64.0% (128)	41.5% (171)		1
A (n=72)	36% (72)	58.5% (241)	0.192	0.79 (0.54-1.17)
LEPR rs1137100 (326A/G)				
AA (n=62)	62.0% (62)	53.9% (111)		1
AG (n=35)	35.0% (35)	42.2% (87)		0.72 (0.41-1.25)
GG (n=3)	3.0% (3)	3.9% (8)	0.401	1.08 (0.25-4.73)
A (n=159)	79.5% (159)	75.0% (309)		1
G (n=41)	20.5% (41)	25.0% (103)	0.218	0.83 (0.53-1.30)
ADIPOQ rs1501299 (276G/T)				
GG (n=49)	49.0% (49)	53.9% (111)		1
GT (n=43)	43.0% (43)	39.3% (81)		1.37 (0.78-2.40)
TT (n=8)	8.0% (8)	6.8% (14)	0.737	1.64 (0.58-4.67)
G (n=141)	70.5% (141)	73.5% (303)		
T (n=59)	29.5% (59)	26.5% (109)	0.429	1.31 (0.86-1.99)

[#] Unadjusted P

[*] Age- and sex-adjusted odds ratio

Table 3 – Influence of the studied polymorphisms in epicardial adipose tissue and abdominal visceral fat volume

	EAT	P *		AVF	P +
LEP rs2167270 (19G/A)					
GG (n=39)	105.36±49.18			155.25±89.67	
GA (n=50)	99.58±60.60			123.64±74.40	
AA (n=11)	95.89±56.78	0.712		130.10±99.83	0.633
G (n=128)	103.10±53.59			142.90±84.78	
A (n=72)	98.45±58.69	0.592		125.61±81.46	0.500
LEPR rs1137100 (326A/G)					
AA (n=62)	99.85±53.24			128.82±73.38	
AG (n=35)	105.96±61.06			154.26±100.97	
GG (n=3)	81.26±41.27	0.750		93.99±42.54	0.292
A (n=159)	101.19±54.75			134.42±80.40	
G (n=41)	102.35±58.46	0.840		145.44±96.50	0.367
ADIPOQ rs1501299 (276G/T)					
GG (n=49)	106.17±53.60			153.17±87.64	
GT (n=43)	95.10±58.27			119.03±72.58	
TT (n=8)	101.59±56.46	0.688		130.53±108.12	0.200
G (n=141)	103.07±54.87			142.76±84.24	
T (n=59)	97.51±56.87	0.429		122.15±81.63	0.268

* Age-, sex- and AVF-adjusted P

+ Age- and sex-adjusted P

EAT – epicardial adipose tissue; AVF – abdominal visceral fat

Table 4 – Influence of studied polymorphism in coronary artery calcification

	CAC=0	CAC>0	P #	OR (95% CI) *
LEP rs2167270 (19G/A)				
GG (n=39)	38.6% (22)	39.5% (17)		1
GA (n=50)	52.6% (30)	46.5% (20)		3.12 (0.79-12.36)
AA (n=11)	8.8% (5)	14% (6)	0.708	9.26 (0.85-101.04)
G (n=128)	64.9% (74)	62.8% (54)		1
A (n=72)	35.1% (40)	37.2% (32)	0.768	1.44 (0.69-3.01)
LEPR rs1137100 (326A/G)				
AA (n=62)	61.4% (35)	62.8% (27)		1
AG (n=35)	35.1% (20)	34.9% (15)		0.31 (0.07-1.34)
GG (n=3)	3.5% (2)	2.1% (1)	0.941	0.26 (0.04-15.07)
A (n=159)	78.9% (90)	80.2% (69)		1
G (n=41)	21.1% (24)	19.8% (17)	0.861	0.42 (0.13-1.31)
ADIPOQ rs1501299 (276G/T)				
GG (n=49)	47.4% (27)	51.2% (22)		1
GT (n=43)	42.1% (24)	44.2% (19)		0.61 (0.05-7.52)
TT (n=8)	10.5% (6)	4.8% (2)	0.677	1.63 (0.44-6.03)
G (n=141)	68.4% (78)	73.3% (63)		1
T (n=59)	31.6% (36)	26.7% (23)	0.532	1.08 (0.43-2.67)

Unadjusted P

* OR (95% CI) Age-, sex- and traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, tabaco use, obesity and family history of cardiovascular disease)-adjusted odds ratio

CAPÍTULO 3: DISCUSSÃO E CONCLUSÃO

3. DISCUSSÃO

Nesta tese propusemo-nos a avaliar a influência de diversos factores que podem ser relevantes na associação entre psoríase e doença cardiovascular e potenciais marcadores de risco clínicos e laboratoriais (analíticos e genéticos) que permitam identificar os doentes em maior risco de desenvolver doença cardiovascular.

Como referido anteriormente, esta discussão encontra-se organizada em 3 partes:

1. Influência de factores comportamentais e de abordagem médica dos doentes com psoríase no risco cardiovascular.
   1.1. Actividade física em doentes com psoríase;
   1.2. Diagnóstico e tratamento dos factores de risco cardiovasculares e prevenção primária de eventos cardiovasculares nos doentes com psoríase.

2. Marcadores de risco cardiovasculares em doentes com psoríase.
   2.1. Disfunção eréctil;
   2.2. Complemento C3;
   2.3. Gordura epicárdica e calcificação coronária.

3. Influência de factores genéticos no desenvolvimento de doença cardiovascular na psoríase.
   3.1. Comorbilidades cardiovasculares na psoríase em idade pediátrica;
   3.2. Biomarcadores genéticos: influência de polimorfismos genéticos da IL-6, TNF-α, leptina, receptor da leptina e adiponectina na gordura epicárdica, gordura visceral abdominal e calcificação arterial coronária em doentes com psoríase.

1. Influência de factores comportamentais e de abordagem médica dos doentes com psoríase no risco cardiovascular

1.1. Actividade física em doentes com psoríase

A influência dos factores de risco de doença cardiovascular associados ao estilo de vida, em especial o exercício físico, tem sido pouco estudada nos doentes com psoríase. Na maioria dos estudos, a actividade física nos doentes com psoríase foi avaliada secundariamente, sem utilizar uma metodologia objectiva e validada e sem um grupo de controlo comparativo. Os resultados destes estudos têm sido contraditórios (106-108), não permitindo estabelecer se os doentes com psoríase praticam de facto menos exercício físico, e demonstrar assim, que também os factores de risco associados ao estilo de vida podem ter um papel no aumento de risco cardiovascular. Contudo, trata-se de uma investigação importante, uma vez que é bem conhecida a importância do exercício físico na prevenção e tratamento da doença cardiovascular e seu o efeito benéfico nos diferentes factores de risco cardiovasculares (109).

Nesta tese, decidimos avaliar a actividade física em doentes com psoríase grave e num grupo controlo sem psoríase, utilizando um instrumento validado, o *International Physical Activity Questionnaire* (Torres T, *et al*. *Levels of Physical Activity in Patients with Severe Psoriasis: A Cross-Sectional Questionnaire Study.* Am J Clin Dermatol. 2014 Apr;15(2):129-35). Os resultados mostraram que os níveis de actividade física dos doentes com psoríase eram significativamente menores do que os do grupo controlo e que, a percentagem de doentes que não cumpria as recomendações para uma actividade física saudável da *American Heart Association* era significativamente maior no grupo de doentes com psoríase. Nestes, os que não cumpriam as recomendações, o risco de serem obesos era significativamente superior relativamente aos que cumpriam. Uma vez que a obesidade tem um papel central na ligação entre psoríase e doença cardiovascular, esta observação reveste-se de particular interesse e reforça a importância do exercício físico nestes doentes.

Estes resultados permitiram demonstrar que, além do risco de doença cardiovascular intrinsecamente associado à psoríase (inflamação sistémica e prevalência aumentada de comorbilidades cardiometabólicas), a actividade física diminuída poderá ser um factor de risco adicional para estes doentes, passível de actuação. A diminuição da actividade física nestes doentes poderá ter um impacto superior ao esperado. Além do efeito positivo que a actividade física tem nas diversas

comorbilidades cardiometabólicas associadas à psoríase, foi demonstrado ter um efeito anti-inflamatório e imunomodulador independente da perda de adiposidade, diminuindo os níveis de diversas citocinas pró-inflamatórias como o TNF-α, IL-6 e INF-γ, influenciando não só a gravidade da psoríase como também o risco de desenvolver doença cardiovascular (110).

As razões pelas quais a actividade física está diminuída nos doentes com psoríase serão variadas, envolvendo provavelmente factores psicológicos e fisiológicos. O impacto que a doença tem na qualidade de vida dos doentes e a estigmatização que provoca, poderá desencorajar a prática de exercício físico. No entanto, a observação de que a gravidade da psoríase, avaliada quer pelo *Body Surface Area* (BSA) quer pelo *Dermatology Life Quality Index* (DLQI), não influenciava a actividade física destes doentes contraria em parte esta hipótese. O impacto cumulativo que a doença tem na vida dos doentes (111) poderá ser uma justificação, explicando a razão pela qual os doentes, apesar de apresentarem uma menor gravidade da doença (por exemplo quando se encontram sob tratamento) continuem a sentir dificuldade em se expor e praticar exercício físico. Relativamente a factores fisiológicos, a psoríase ao interferir com a termorregulação e transpiração, poderá limitar os níveis de actividade física nestes doentes (112).

Este estudo, reforça a necessidade de incluir na abordagem dos doentes com psoríase, uma avaliação da actividade física e o incentivo para a adopção de um estilo de vida saudável, que inclua uma actividade física regular.

1.2. Diagnóstico e tratamento dos factores de risco cardiovasculares e prevenção primária de eventos cardiovasculares nos doentes com psoríase

Vários estudos têm demonstrado que a psoríase é um factor de risco independente de doença cardiovascular, especialmente nas formas mais graves, provavelmente decorrente da inflamação sistémica (32-34, 36, 113). Recentemente foi estimado que a psoríase grave poderá aumentar em 6.2% o risco de eventos cardiovasculares a 10 anos (36).

Um importante factor que pode influenciar o risco cardiovascular dos doentes com psoríase é o subdiagnóstico e subtratamento dos factores de risco cardiovasculares (FRCV) assim como uma menor prevenção primária dos eventos cardiovasculares. De facto, o diagnóstico e o correcto tratamento dos FRCV e a prevenção primária de eventos cardiovasculares são essenciais para a diminuição da morbilidade e

mortalidade cardiovascular (114). Numa população de maior risco, como é o caso dos doentes com psoríase, este factor reveste-se ainda de maior importância.

Neste contexto decidimos avaliar a taxa de subdiagnóstico e de subtratamento dos FRCV numa população com psoríase grave (*Poster*: Torres, *et al*. *Cardiovascular risk factors in patients with severe psoriasis: are they being well screened and treated? A real-world setting study.* 4th Congress of the Psoriasis International Network, Julho 2013; Dados não publicados).

Observámos que, dos doentes com HTA, DM e hipercolesterolemia, 38.8%, 15.4% e 36.1% respectivamente, estavam por diagnosticar. Dos doentes com diagnóstico prévio de HTA e hipercolesterolemia, 13.3% e 38.9% não se encontravam medicados, pelo que, apenas os doentes com diagnóstico de DM estavam todos sob tratamento. Adicionalmente observámos que os doentes sob tratamento para os FRCV, 76.7%, 46.2% e 65.2% não se encontravam correctamente controlados (objectivos terapêuticos não alcançados) para HTA, DM e hipercolesterolemia respectivamente, de acordo com as recomendações actuais. Finalmente, avaliámos o subgrupo de doentes de maior risco, isto é, com uma FRS>20%, correspondente a 16.5% dos doentes. Apenas 11.8% destes doentes se encontravam devidamente controlados para os três FRCV (HTA: 76.5%; DM: 35.3%; hipercolesterolemia: 35.3%) e apenas 17.6% e 41.2% recebiam tratamento com aspirina e estatina respectivamente como prevenção primária de doença cardiovascular.

Dados semelhantes foram observados nos doentes incluídos nos ensaios clínicos do ustekinumab (115). Apesar do conhecimento crescente da associação entre psoríase e risco cardiovascular, uma proporção elevada dos doentes com psoríase grave não é submetida a uma prevenção cardiovascular correcta, e apesar de ser conhecido que este problema é transversal a várias áreas da medicina, os doentes com psoríase têm um risco superior de doença cardiovascular, pelo que a prevenção deverá ser reforçada.

Um outro factor deve ser ainda considerado nos doentes com psoríase. As recomendações actuais para os objectivos terapêuticos no tratamento dos FRCV e de necessidade de instituição de prevenção primária de eventos cardiovasculares têm em conta o risco cardiovascular conferido pelo FRS, diferindo entre os doentes de baixo, médio ou alto risco (116-118). O FRS prevê o risco de eventos cardiovasculares *major* e de doença coronária, avaliando diversos FRCV, como a idade, sexo, níveis séricos de colesterol, diagnóstico de HTA, pressão arterial

sistólica, diabetes e tabaco (118). No entanto, é motivo de debate a existência de outros factores, não avaliados no FRS, que poderão contribuir para o aumento de risco de doença coronária e de eventos cardiovasculares, em particular a inflamação crónica (114, 120). Assim, é possível que as recomendações existentes, direccionadas à população geral, não se adeqúem aos doentes com psoríase, uma vez que o FRS poderá subestimar o risco de doença cardiovascular nestes doentes, por não ter em conta o risco atribuível à doença (6.2%). Por esta razão, é provável que mesmo os doentes correctamente tratados, não se encontrem a fazer a prevenção adequada, influenciando o risco de desenvolver doença cardiovascular.

Assim, avaliamos o impacto da adição do risco cardiovascular atribuível à psoríase grave (FRS=6.2%), no tratamento dos factores de risco cardiovasculares e na instituição de prevenção primária de doença cardiovascular (Torres T, *et al*. *Framingham Risk Score underestimates cardiovascular disease risk in severe psoriatic patients: Implications in cardiovascular risk factors management and primary prevention of cardiovascular disease*. J Dermatol. 2013 Nov;40(11):923-6).

Observámos que 57% dos doentes estudados foram reclassificados numa categoria superior de risco. Após esta reclassificação, 28% e 42% dos doentes considerados correctamente tratados para HTA e hipercolesterolemia respectivamente, foram considerados subtratados, uma vez que não atingiam os objectivos terapêuticos propostos pelas recomendações. Adicionalmente, de todos os doentes reclassificados para alto risco (isto é, com necessidade de prevenção primária de eventos cardiovasculares com aspirina e estatina), nenhum se encontrava medicado com aspirina e apenas 40% estava medicado com estatina.

Os resultados do nosso estudo mostraram que, devido ao risco inerente à psoríase grave, os doentes com psoríase deverão ser considerados e classificados como doentes de maior risco cardiovascular, comparativamente com a população geral com iguais características, e que por esta razão os FRCV deverão ser tratados de uma forma mais agressiva. Adicionalmente, as recomendações actuais para o tratamento dos FRCV e para prevenção de doença cardiovascular poderão não se adequar à população com psoríase grave. De facto, as sociedades científicas que elaboram as diferentes recomendações de diagnóstico e tratamento dos FRCV já reconheceram que existem outros factores de risco a ter em conta que não são capturados pelo FRS, em especial a inflamação sistémica (114). No caso da artrite reumatóide, a *European League Against Rheumatism* (EULAR) já propôs novas recomendações para a abordagem do risco cardiovascular nestes doentes, tendo

em conta o risco atribuível à doença e a necessidade de objectivos terapêuticos mais apertados no tratamento dos FRCV (121). Contudo, no caso da psoríase, este processo não foi ainda iniciado.

Assim, os resultados apresentados nestes estudos reforçam a importância do diagnóstico e tratamento dos FRCV numa população de risco cardiovascular acrescido, como é a psoriática, assim como da necessidade de recomendações adequadas a esta população.

2. Marcadores de risco cardiovasculares em doentes com psoríase

2.1. Disfunção eréctil

Mais de metade das mortes súbitas de causa cardiovascular ocorre em doentes sem diagnóstico prévio, demonstrando a importância da identificação da doença cardiovascular assintomática (122). A disfunção eréctil é um potencial marcador clínico de risco cardiovascular. De facto, foi demonstrado que a disfunção eréctil é um preditor independente de doença cardiovascular (123, 124), incluindo doença arterial coronária (125) e AVC (126,127), com os sintomas de disfunção eréctil a precederem em média 2 a 3 anos a sintomatologia da doença coronária e em 3 a 5 anos os eventos cardiovasculares (128). Assim, actualmente considera-se que a presença de disfunção eréctil tem um valor preditivo de eventos cardiovasculares comparável ou superior a alguns FRCV tradicionais (129). Além disso, a gravidade da disfunção eréctil também se correlaciona com a gravidade da doença aterosclerótica (130), tendo sido demonstrado, por exemplo, uma correlação significativa entre a gravidade de disfunção eréctil, avaliada pelo questionário *International Index of Erectile Function* (IIEF), e a calcificação arterial coronária avaliada por tomografia computorizada multidetectores (131). Embora a função eréctil normal seja um evento neurovascular, influenciado por factores hormonais e psicológicos, a integridade e função endotelial tem um papel fundamental na fisiologia da erecção peniana, através da libertação de óxido nítrico e outros factores endoteliais (132), pelo que actualmente a disfunção endotelial é considerada o elo de ligação entre disfunção eréctil e doença cardiovascular (133, 134). Devido ao menor calibre dos vasos penianos, as manifestações clínicas de disfunção endotelial e aterosclerose são mais precoces a nível peniano do que a nível coronário ou cerebral, pelo que a disfunção eréctil é considerada um marcador precoce de disfunção endotelial e aterosclerose (130, 135).

A inflamação sistémica é uma importante causa de disfunção endotelial, pelo que é provável que patologias associadas a um estado inflamatório sistémico, como a psoríase, se associem a disfunção eréctil. Estudos anteriores documentaram uma prevalência aumentada de disfunção eréctil em doentes com psoríase (136-140). No entanto, a maioria destes trabalhos focalizaram-se essencialmente no componente psicológico da doença e o seu impacto a nível sexual, demonstrando que a ansiedade e depressão associadas à psoríase e especialmente a presença de lesões genitais eram importantes determinantes na presença de disfunção sexual nos doentes com psoríase (136, 138-140). Em apenas um estudo, envolvendo doentes com diferentes graus de gravidade de psoríase, os FRCV foram também avaliados, no qual a idade e a presença de HTA demonstraram ser um factor de risco independente de disfunção eréctil mas não o diagnóstico de psoríase (137).

Assim, decidimos avaliar e comparar a prevalência e gravidade de disfunção eréctil entre doentes com psoríase grave e uma população sem psoríase. Para isso, utilizámos o questionário IIEF e homogeneizámos as amostras excluindo doentes com psoríase ligeira, artrite psoriática e história prévia de doença cardiovascular. Em colaboração com o Serviço de Dermatologia do Centro Hospitalar de Lisboa Central avaliámos um total de 135 doentes com psoríase grave e 201 doentes com outras patologias dermatológicas, não inflamatórias e sem envolvimento genital (Cabete J*, Torres T*, *et al*. *Erectile dysfunction in psoriasis patients*. Eur J Dermatol 2014). Constatámos que a presença de psoríase grave se associava a uma maior prevalência e gravidade de disfunção eréctil, independentemente da idade, sexo e FRCV tradicionais e que, na análise multivariada, a psoríase constituía um factor de risco independente de disfunção eréctil. Observámos, ainda, que o impacto na qualidade de vida dos doentes (avaliado pelo DLQI) e a presença de lesões genitais não contribuíam para a disfunção eréctil nos doentes com psoríase, sugerindo que, pelo menos nestes doentes, os factores psicológicos não eram determinantes, apontando para uma possível associação entre a presença de aterosclerose subclínica e disfunção eréctil nos doentes com psoríase. Uma limitação relevante do estudo foi a não inclusão de marcadores analíticos de inflamação/aterosclerose ou exames de imagem de avaliação de aterosclerose e/ou circulação sanguínea peniana, que permitiriam avaliar com maior detalhe esta possível ligação entre a psoríase, disfunção eréctil e aterosclerose subclínica. Os resultados deste estudo reforçam os dados anteriormente publicados de que a psoríase se associa a uma prevalência aumentada de disfunção eréctil e que poderá ser um factor de

risco independente, sendo a aterosclerose o elo de ligação, provavelmente decorrente da inflamação sistémica.

Assim, dado que a disfunção eréctil precede a doença cardiovascular estabelecida, a avaliação da sua presença em doentes do sexo masculino com psoríase poderá funcionar como um marcador precoce de doença cardiovascular, permitindo assim identificar os doentes em maior risco e uma intervenção mais precoce.

2.2. Complemento C3

A procura de biomarcadores preditores de doença cardiovascular tem sido extensa e vários marcadores inflamatórios têm sido estudados (141). A proteína C-reactiva (PCR) foi o mais estudado, tendo sido demonstrado que os seus níveis se relacionam com o risco de doença cardiovascular (142, 143). Na psoríase, o papel da PCR como biomarcador de doença cardiovascular também foi extensamente estudado, tendo sido consistentemente demonstrado que a psoríase se associa a níveis mais elevados de PCR (144). No entanto, a PCR não se encontra elevada apenas na doença cardiovascular, estando aumentada noutras situações, particularmente nas infecções agudas e/ou crónicas, pelo que é fundamental encontrar biomarcadores mais específicos.

O C3 tem sido proposto como um factor de risco de doença cardiovascular, tendo sido demonstrado que participa no desenvolvimento de aterosclerose e se encontra presente nas placas arterioscleróticas (145, 146). Nos últimos anos, vários estudos demonstraram que os níveis de C3 são preditores de EAM, se encontram elevados nos doentes com doença cardiovascular e se associam a insulino-resistência (147-150). Adicionalmente, muitos destes estudos demonstraram que o C3 é um marcador de risco de doença cardiovascular e de insulino-resistência mais específico do que a PCR (151, 152).

A informação na literatura sobre o papel do C3 na psoríase é muito escassa. Alguns estudos indicam que o C3 poderá fazer parte da inflamação sistémica da psoríase, uma vez que os seus níveis séricos estão elevados, além de que se observou que o C3 é expresso nas lesões psoriáticas (153, 154). Contudo, a sua influência no risco cardiometabólico e cardiovascular na psoríase nunca foi estudado.

Assim, procurámos esclarecer o papel do C3 no risco cardiometabólico na psoríase e se poderia funcionar como um melhor marcador de risco do que a PCR (Torres T, *et al*. *Complement C3 as a marker of cardiometabolic risk in psoriasis*. Arch Dermatol Res. 2014 May 22).

Observámos que a psoríase se associava a níveis séricos de C3 significativamente mais elevados comparativamente com os da população controlo e que este aumento era independente do perímetro abdominal, isto é, do excesso de adiposidade central. O C3 é produzido essencialmente no fígado, mas também é sintetizado por macrófagos activados e adipócitos (155). De facto, níveis elevados de C3 têm sido associados a excesso de adiposidade (156). Também em indivíduos obesos se observou um aumento da expressão de mRNA do C3 no tecido adiposo visceral, provavelmente devido à sua infiltração por macrófagos activados e à disfunção dos adipócitos características da obesidade (157). No entanto, apesar da associação entre excesso de tecido adiposo e níveis elevados de C3, no nosso estudo, observámos que esta relação nos doentes com psoríase era independente do excesso de adiposidade. Este facto, aponta para a possibilidade de o aumento de C3 na psoríase não ser mediada apenas pelo excesso de adiposidade presente nestes doentes, mas igualmente por outros mecanismos fisiopatogénicos da doença. De facto, o estado inflamatório da psoríase poderá explicar em parte o aumento do C3. Foi demonstrado que várias citocinas pró-inflamatórias presentes na psoríase, como TNF-α,IL-1β, IL-6, e INF-γ aumentam a produção de C3 por várias células, incluindo os hepatócitos, adipócitos e macrófagos (158). Assim, é possível que o estado pró-inflamatório da psoríase promova a produção de C3. Uma outra fonte de C3 poderá ser a sua produção pelos queratinócitos (153).

Outra importante observação neste estudo foi a demonstração de que, nos doentes com psoríase, os níveis de C3 poderão representar um melhor marcador de risco cardiometabólico do que a PCR. Ao contrário desta, observou-se uma associação entre os níveis de C3 com insulino-resistência, presença de síndrome metabólico e LDL-oxidado, de uma forma independente da gordura visceral abdominal (quantificada por TCMD). De facto, os níveis mais elevados de PCR na psoríase poderão dever-se essencialmente à obesidade observada nestes doentes, devido à estimulação hepática pela IL-6 produzida pelo tecido adiposo (151). Pelo contrário, os níveis de C3 reflectem também a inflamação sistémica, uma vez que a sua produção hepática é induzida por citocinas que se encontram aumentadas na psoríase, como a IL-1β e TNF-α, que têm um papel conhecido na promoção de insulino-resistência através da interferência com o receptor de insulina (159).

Assim, as principais conclusões deste estudo são que os níveis de C3 se encontram aumentados na psoríase, não só devido ao excesso de adiposidade observada nestes doentes, mas provavelmente também pelo estado inflamatório da doença.

Adicionalmente, nos doentes com psoríase, o C3 demonstrou ser um melhor marcador de risco cardiometabólico do que a PCR, especialmente de insulino-resistência, presença de síndrome metabólico e de perfil lipídico aterogénico.

Este estudo demonstrou que o C3 poderá ser utilizado como um biomarcador de risco cardiometabólico na psoríase, permitindo identificar os doentes de maior risco.

2.3. Gordura epicárdica e calcificação coronária

É provável que além da inflamação sistémica e da prevalência aumentada de FRCV, existam outros factores que contribuam para o aumento do risco de doença cardiovascular na psoríase.

A gordura epicárdica é um tipo de tecido adiposo visceral que envolve o coração e a vascularização coronária (160). Apesar de constituir apenas 1% do tecido adiposo corporal, a gordura epicárdica parece ser um factor importante no desenvolvimento de doença arterial coronária, devido à proximidade com os vasos coronários, através da produção local de diversas citocinas e adipocinas pró-inflamatórias, como o TNF-α, IL-6, leptina e MCP-1(161-163). De facto, a gordura epicárdica mostrou associar-se ao desenvolvimento de aterosclerose, doença arterial coronária, insulino-resistência e síndrome metabólico (164-166). Adicionalmente foi demonstrado que a gordura epicárdica é um marcador preditivo de eventos cardiovasculares independentemente dos FRCV e índice de massa corporal (167, 168).

Desta forma, decidimos avaliar e comparar com uma população controlo, o volume de gordura epicárdica e a sua relação com aterosclerose coronária (por quantificação da calcificação arterial coronária) numa população com psoríase grave (Torres T, *et al. Epicardial adipose tissue and coronary artery calcification in psoriasis patients.* J Eur Acad Dermatol Venereol. 2014 Apr 21).

Existem diversas técnicas de imagem para avaliação da gordura epicárdica, como a ressonância magnética, a tomografia computorizada e a ecocardiografia. Contudo a ressonância magnética e a tomografia computorizada são consideradas as técnicas *gold standard*, por permitirem a quantificação volumétrica e não a avaliação da área ou espessura da gordura epicárdica como ocorre com a ecocardiografia (169-171). A quantificação da calcificação arterial coronária (CAC) é uma forma não invasiva de avaliação de aterosclerose subclínica, extremamente sensível, tendo sido demonstrado que é um melhor marcador preditivo de eventos

cardiovasculares futuros do que a medição da espessura da camada intima média carotídea (172, 173). Assim, neste estudo, optamos pela TCMD, uma vez que permite a avaliação simultânea da gordura epicárdica, da gordura visceral abdominal e da CAC. A avaliação da gordura visceral abdominal era essencial, uma vez que é o melhor marcador de excesso de adiposidade visceral (comparativamente com medidas indirectas como o índice de massa corporal (IMC) ou o perímetro abdominal), permitindo compreender a relação da gordura epicárdica com o excesso de gordura visceral, que se sabe estar aumentada na psoríase (46).

Na avaliação efectuada, observámos que o volume de gordura epicárdica estava significativamente aumentado nos doentes com psoríase comparativamente com a população controlo, de forma independente da gordura visceral abdominal. Adicionalmente, e de acordo com a evidência na literatura, a psoríase demonstrou ser um factor de risco independente de aterosclerose (62, 174), uma vez que se associou a um risco aumentado de CAC, independentemente da idade, sexo, FRCV e volume de gordura visceral. Por fim, nos doentes com psoríase, o volume de gordura epicárdica correlacionou-se com a presença de aterosclerose, de forma independente (idade, sexo, FRCV, gordura visceral abdominal e duração da psoríase), mostrando que tem um papel no desenvolvimento de aterosclerose coronária nos doentes com psoríase.

Assim, estes resultados são a favor de que a gordura epicárdica poderá ser utilizada como um preditor independente de aterosclerose coronária em doentes com psoríase, sugerindo a existência de um outro mecanismo, para além da inflamação sistémica e FRCV, responsável pela associação entre psoríase e a aterosclerose coronária.

Alguns estudos recentes obtiveram resultados semelhantes, embora em amostras mais pequenas, envolvendo entre 31 e 60 doentes, e utilizando outras técnicas de avaliação da gordura epicárdica, como a ecocardiografia (175-177). No entanto, é de salientar que em nenhum desses estudos foi avaliada a gordura abdominal visceral.

Não é ainda conhecida a causa do aumento da gordura epicárdica nos doentes com psoríase, sendo provavelmente multifactorial, envolvendo factores genéticos, imunológicos e ambientais. No que diz respeito aos factores genéticos, a expressão de muitas citocinas é influenciada por polimorfismos dos seus genes, contribuindo para o desenvolvimento de doenças inflamatórias como a psoríase (178), mas

também para o excesso de adiposidade (179, 180). Entre estas citocinas encontra-se a IL-6 que tem um papel importante na patogenia da psoríase (84, 85) mas também no excesso de adiposidade/obesidade e aterosclerose (88, 90). Neste projecto de investigação, demonstrámos também que a presença do alelo G do polimorfismo genético rs2069840 [-1753C/G] da IL-6 se associava a um aumento do volume de gordura epicárdica nos doentes com psoríase, apontando para uma possível contribuição genética (Torres T, *et al. Influence of IL-6 gene polymorphisms on epicardial adipose tissue and coronary artery calcification in psoriasis patients.* Br J Dermatol. 2014). Além disso, a produção de mediadores inflamatórios pela gordura epicárdica poderá ser aumentada em resposta à inflamação sistémica da psoríase, pela estimulação dos adipócitos por algumas da citocinas pró-inflamatórias que se encontram em níveis aumentados na psoríase, como o TNF-α e a IL-6 (26, 43). Por fim, o estilo de vida menos saudável e a diminuição da actividade física associados à psoríase, poderão contribuir igualmente para o aumento da gordura epicárdica, uma vez que a perda de peso e o exercício aeróbico mostraram estar associados à sua diminuição (181, 182). Estes dados reforçam a importância da adopção de uma estilo de vida saudável, incluindo exercício físico regular.

Assim, a gordura epicárdica é provavelmente mais um importante factor que contribui para o aumento do risco cardiovascular nos doentes com psoríase, particularmente importante devido ao efeito local na vascularização miocárdica.

3. Influência de factores genéticos no desenvolvimento de doença cardiovascular na psoríase

3.1. Comorbilidades cardiovasculares na psoríase em idade pediátrica

Existe alguma evidência clínica que sugere que o risco cardiovascular nos doentes com psoríase poderá ser em parte geneticamente determinado. No entanto, existem ainda poucos estudos nesta área. Gisondi et al, demonstrou que a prevalência de história familiar de doença cardiovascular estava aumentada na psoríase comparativamente à população controlo, em particular uma maior prevalência de história familiar materna de EAM e história familiar paterna de AVC (183). Por outro lado, Mallbris et al, avaliou o perfil lipídico de doentes com psoríase diagnosticada há menos de 1 ano e observou que, numa fase inicial da doença, o perfil lipídico se encontrava alterado comparativamente com o grupo controlo (107). Finalmente, a presença de comorbilidades cardiometabólicas em doentes

com psoríase em idade pediátrica indicia igualmente que poderá existir uma influência genética nesta associação. No entanto, embora esteja bem descrita na população adulta a associação entre psoríase, comorbilidades cardiometabólicas e doença cardiovascular, a sua evidência na população pediátrica é ainda limitada, tendo sido demonstrado em alguns estudos que a prevalência de FRCV e de síndrome metabólico também se encontra aumentada na psoríase em idade pediátrica (184-187).

Neste sentido, e sendo um dos objectivos desta tese avaliar a influência genética no desenvolvimento de doença cardiovascular, decidimos analisar numa população pediátrica com psoríase (6-14 anos) a presença de comorbilidades cardiometabólicas e de síndrome metabólico, comparativamente com uma população controlo.

Nesse estudo (Torres *et al. Cardiovascular comorbidities in childhood psoriasis*. Eur J Dermatol. 2014 Apr 1;24(2):229-35) observámos que as crianças com psoríase tinham um aumento da prevalência de excesso de adiposidade (usando o IMC como marcador) e de adiposidade central (usando como marcadores o perímetro abdominal e rácio perímetro abdominal/altura) comparativamente com a população controlo. Adicionalmente, observou-se uma tendência para um aumento da prevalência de síndrome metabólico nos doentes com psoríase, com dois dos seus componentes (pressão arterial e perímetro abdominal) encontrando-se significativamente aumentados. Finalmente observou-se também um perfil lipídico alterado nas crianças com psoríase, com níveis séricos de LDL-oxidado e Apolipoproteína B aumentados comparativamente com o grupo controlo, independentemente do excesso de adiposidade. Com estes resultados, reforçamos a evidência científica de que a associação com comorbilidades cardiometabólicas já conhecida na psoríase em idade adulta também se verifica em idade pediátrica, indicando que provavelmente também o componente genético influencia o desenvolvimento de doença cardiovascular nos doentes com psoríase.

Este estudo tem ainda duas importantes implicações: realça, por um lado, a importância de, tal como nos doentes em idade adulta, se efectuar um rastreio e tratamento das comorbilidades cardiovasculares nas crianças com psoríase e se promover um estilo de vida saudável, com o objectivo de diminuir, desde o início da doença, o risco de doença cardiovascular; por outro lado, realça a importância da investigação de marcadores genéticos responsáveis por esta associação.

3.2. Biomarcadores genéticos: influência de polimorfismos genéticos da IL-6, TNF-α, leptina, receptor da leptina e adiponectina na gordura epicárdica, gordura visceral abdominal e calcificação arterial coronária em doentes com psoríase

Várias citocinas pró-inflamatórias, adipocinas e factores pró-angiogénicos foram implicados na patogenia da psoríase, da aterosclerose e de comorbilidades cardiometabólicas, incluindo o TNF-α, IL-6, VEGF, leptina, resistina, adiponectina ou endotelina-1 (42, 48, 188). A expressão de muitas destas citocinas e adipocinas é influenciada por polimorfismos dos seus genes, podendo contribuir para o desenvolvimento de doenças inflamatórias como a psoríase(178, 189-191), mas também de aterosclerose, excesso de adiposidade ou outras comorbilidades (192-194). A informação existente relativa à associação entre genes implicados no desenvolvimento da inflamação da psoríase e a presença de comorbilidades e aterosclerose é ainda limitada. Assim, decidimos avaliar a influência de SNPs de genes destes mediadores (IL-6, TNF-α, Leptina e Adiponectina) no desenvolvimento de aterosclerose (através da avaliação da calcificação arterial coronária) ou de comorbilidades cardiometabólicas em doentes com psoríase grave.

Avaliámos a influência de 4 polimorfismos genéticos da IL-6 (rs1800795 [-174G/C], rs1800796 [-572G/C], rs2069827 [-1426G/T] e rs2069840 [-1753C/G]) no volume de gordura epicárdica e no desenvolvimento de aterosclerose coronária nos doentes com psoríase grave (Torres T, *et al. Influence of IL-6 polymorphisms on epicardial adipose tissue and coronary artery calcification in psoriasis patients*. Br J Dermatol. 2014).

A IL-6 foi implicada na patogenia da psoríase (27, 84-86), assim como da obesidade(87, 88), aterosclerose e doença cardiovascular (90, 91). Alguns polimorfismos do seu gene podem influenciar a sua expressão (104, 195) e contribuir quer para o desenvolvimento de psoríase (178, 196) quer para o excesso de adiposidade (197, 198), aterosclerose e doença cardiovascular (199). O polimorfismo genético da IL-6 mais estudado até ao momento foi o rs1800795 [-174G/C] que se localiza na região promotora do gene e influencia a transcrição e os níveis séricos da citocina (104, 200). Existem outros locais polimórficos no gene da IL-6 que parecem ser funcionais e que influenciam a transcrição genética, como é o caso dos polimorfismos rs1800796 [-572G/C], rs2069827 [-1426G/T] e rs2069840 [-1753C/G] embora tenham sido menos explorados até ao momento. No entanto, os resultados dos estudos conhecidos com estes polimorfismos têm sido contraditórios, uma vez que nem todos demonstraram uma associação com

excesso de adiposidade ou com maior expressão de IL-6 (104, 200-203). É possível que o efeito dos polimorfismos da IL-6 na sua expressão assim como o efeito da própria IL-6 possa variar entre patologias ou mesmo entre o tipo de células implicadas.

Observámos que a presença do alelo G do polimorfismo rs2069840 [-1753C/G] do gene da IL-6 nos doentes com psoríase se associou a um aumento do volume de gordura epicárdica, de forma independente da idade, sexo e gordura visceral abdominal. Este efeito estava aumentado nos doentes homozigóticos para o alelo G (GG), uma vez que apresentavam um volume superior de gordura epicárdica comparativamente com o dos doentes com os genótipos CC+CG. Contudo, nenhum dos polimorfismos estudados se associou a um aumento do risco de desenvolvimento de calcificação arterial coronária, que poderá ser explicado em parte pelo facto da aterosclerose ser uma doença poligénica e um único SNP não ser suficiente para explicar o desenvolvimento de doença aterosclerótica. Adicionalmente, neste grupo de doentes não se observou nenhuma diferença relativamente à presença dos polimorfismos genéticos estudados comparativamente com a população controlo, indicando que provavelmente, mais do que uma contribuição genética, existem outros factores e outras vias inflamatórias que definem os níveis de IL-6 nos doentes com psoríase.

A forma como este polimorfismo da IL-6 influencia a gordura epicárdica é desconhecida. É possível que certos genótipos se associem a um menor consumo de energia, levando a um aumento de tecido adiposo a longo prazo (198, 204, 205). Por outro lado, este polimorfismo poderá associar-se a uma maior expressão de IL-6 (195, 202) sendo conhecida a influência da IL-6 na gordura visceral, promovendo o recrutamento e activação de macrófagos e estimulando os adipócitos a produzir diversos mediadores inflamatórios, como MCP-1, e diversas adipocinas que aumentam e perpetuam a inflamação e promovem o excesso de adiposidade (43, 48). No entanto, a razão deste aumento ser independente do excesso de adiposidade global é igualmente difícil de explicar. De facto, mostrámos num outro trabalho (Torres T, *et al. Epicardial adipose tissue and coronary artery calcification in psoriasis patients.* J Eur Acad Dermatol Venereol. 2014 Apr 21), que a psoríase se associa a um aumento do volume de gordura epicárdica, independentemente da gordura visceral abdominal. Esta situação poderá ser explicada por alguma diferença fisiológica entre a gordura epicárdica e a gordura visceral abdominal, nomeadamente uma expressão genética diferente. De facto, num estudo recente foi demonstrado que os adipócitos epicárdicos diferem dos adipócitos viscerais,

exibindo um fenótipo pró-inflamatório mesmo em condições basais, uma vez que, os pré-adipócitos epicárdicos mostraram uma expressão aumentada de IL-6 e IL-8 comparativamente com os pré-adipócitos viscerais (206), apesar da gordura epicárdica e gordura visceral abdominal partilharem a mesma origem embrionária (207).

Este estudo foi o primeiro a avaliar a influência de polimorfismos genéticos da IL-6 no volume de gordura epicárdica e na calcificação arterial coronária em doentes com psoríase. Envolveu uma amostra homogénea, incluindo apenas doentes com psoríase grave, sem artrite psoriática e sem doença cardiovascular, e com uma caracterização clínica, analítica e imagiológica detalhada. No entanto, apresenta algumas limitações como a metodologia *cross*-sectional e observacional e o tamanho da amostra (208). Além disso, uma avaliação de haplótipos poderia fornecer mais informação, comparativamente com a avaliação do efeito de SNPs individuais. A limitação mais importante foi provavelmente a não avaliação dos níveis de IL-6, o que condicionou a compreensão das implicações funcionais dos polimorfismos estudados. No entanto, é bem conhecida a dificuldade de medição dos níveis da IL-6, que podem não reflectir o significado biológico a nível tecidual e explicar os resultados contraditórios em muitos estudos (209).

Desta forma, estes resultados indicam uma possível contribuição do gene da IL-6 no desenvolvimento de excesso de adiposidade, em particular de gordura epicárdica, nos doentes com psoríase. Se replicados, estes resultados poderão ter importância clínica e implicações práticas relevantes, permitindo a identificação dos doentes em maior risco de desenvolver doença cardiovascular, com uma consequente abordagem individualizada e personalizada.

Avaliámos também a influência de 3 polimorfismos do TNF-α (rs361525 [-238G/A], rs1800629 [-308G/A] e rs1799964 [-1031T/C]) no desenvolvimento de aterosclerose, avaliada por calcificação arterial coronária (Torres T, *et al. Influence of TNF-α gene polymorphisms in coronary artery calcification in psoriasis patients.* J Eur Acad Dermatol Venereol. 2014).

O TNF-α é uma citocina pró-inflamatória que foi implicada na patogénese da psoríase e aterosclerose (8, 92), tendo um efeito deletério nas células endoteliais, promovendo disfunção e lesão endotelial (92). A sua síntese é, em grande parte, regulada geneticamente, tendo sido estimado que factores genéticos poderão ser responsáveis por 60% da variabilidade da produção de TNF-α (210). De facto, a transcrição e produção de TNF-α pode ser regulada por vários SNPs presentes

na região promotora no gene. Por exemplo, foi demonstrado que a presença do alelo A do polimorfismo rs1800629 [-308G/A] se associa a um aumento de cerca de 6 vezes da expressão do gene e a níveis aumentados de TNF-α (189). Alguns destes polimorfismos foram estudados na psoríase e na doença cardiovascular, embora com resultados contraditórios (189, 192, 211). As variantes genéticas rs361525 [-238G/A] e rs1800629 [-308G/A] foram as mais estudadas na psoríase, embora os resultados não tenham sido sempre concordantes. Uma meta-analise recente mostrou que o polimorfismo rs1800629 [-308G/A] se associa a um menor risco de desenvolver psoríase, enquanto a variante rs361525 [-238G/A] a um maior risco(189). No caso do polimorfismo rs1799964 [-1031T/C], o seu estudo na psoríase é ainda limitado e igualmente com resultados contraditórios (212, 213), com apenas um estudo a demonstrar uma associação deste polimorfismo com psoríase (213). Relativamente à associação entre polimorfismos do TNF-α e doença cardiovascular (EAM e AVC), também os resultados dos estudos têm sido contraditórios (192, 211).

No nosso estudo, não se observou uma associação entre os polimorfismos estudados e a presença de calcificação arterial coronária. Adicionalmente, não foi observada nenhuma diferença na frequência genotípica e alélica entre os doentes com psoríase e os controlos, mostrando que, pelo menos neste grupo de doentes, nenhum dos polimorfismos era um factor de risco de desenvolvimento de psoríase. Uma importante limitação foi a ausência de medição dos níveis séricos de TNF-α, uma vez que não permitiu avaliar as consequências funcionais dos polimorfismos estudados.

Existem várias explicações possíveis para estes resultados, entre os quais o tamanho da amostra. Além disso, os níveis séricos de TNF-α podem ser afectados por múltiplos factores, genéticos e ambientais, pelo que é possível que sejam necessários factores adicionais para promover aterosclerose mediada por TNF-α. Adicionalmente, a aterosclerose é uma doença poligénica, pelo que um único SNP poderá não ser suficiente para explicar o desenvolvimento de aterosclerose.

Assim, estes resultados, apesar de negativos, poderão ter influência e implicações em estudos futuros.

Finalmente, avaliámos ainda a influência de polimorfismos da leptina (LEP rs2167270 [19 G/A]), do receptor da leptina (LEPR rs1137100 [326 A/G]) e da adiponectina (ADIPOQ rs1501299 [276G/T]) no volume de gordura epicárdica, gordura visceral abdominal e desenvolvimento de aterosclerose (Torres T, *et*

al. Lack of association between leptin, leptin receptor and adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat and atherosclerotic burden in psoriasis patients).

A leptina e a adiponectina são adipocinas que têm sido apontadas como tendo um possível papel na ligação fisiopatológica entre a psoríase, comorbilidades associadas à psoríase, em particular a obesidade, e doença cardiovascular (42). Os níveis plasmáticos desta adipocinas são fortemente influenciados por polimorfismos dos seus genes, no caso da adiponectina em cerca de 30-50% (103), tendo alguns estudos mostrado uma associação entre polimorfismos genéticos da leptina, do seu receptor e da adiponectina e o desenvolvimento de obesidade e de doença cardiovascular (103, 214, 215). O polimorfismo LEP rs2167270 [19 G/A] mostrou associar-se a obesidade e a níveis aumentados de leptina enquanto a variante genética do receptor da leptina, LEPR rs1137100 [326 A/G], se associou a excesso de adiposidade (214, 215). No entanto, o estudo do papel dos polimorfismos destas adipocinas na psoríase é ainda muito limitado. De facto, não existem estudos na psoríase avaliando variantes genéticas da adiponectina e do receptor da leptina e, no caso da leptina, apenas quatro estudos avaliaram polimorfismo desta adipocina. A variante LEP rs7799039 [-2548G/A] mostrou associar-se a psoríase em um dos estudos (216), enquanto em outros dois não se observou diferença entre os doentes com psoríase e a população controlo (217, 218). Recentemente um outro polimorfismo, LEP rs2060713, foi investigado, não tendo sido encontrada nenhuma associação com psoríase (191).

No nosso estudo, não foi observada nenhuma associação entre os polimorfismos avaliados e o volume de gordura epicárdica, abdominal visceral ou a presença de calcificação coronária, assim como nenhuma relação com os níveis de leptina. De acordo com estudos publicados não foi observada nenhuma diferença na frequência genotípica e alélica entre os doentes com psoríase e os controlos, mostrando que, pelo menos neste grupo de doentes, nenhum dos polimorfismos era um factor de risco de desenvolvimento de psoríase.

Apesar destes resultados negativos, não está excluída a implicação destas adipocinas na ligação fisiopatológica entre a psoríase e as suas comorbilidades, pelo que outros polimorfismos destes genes deverão ser investigados no futuro.

Na tabela seguinte encontram-se resumidos os resultados e principais conclusões da investigação efectuada.

INFLUÊNCIA DE FACTORES COMPORTAMENTAIS E DE ABORDAGEM MÉDICA DOS DOENTES COM PSORÍASE NO RISCO CARDIOVASCULAR	
Publicação	**Resultados/Conclusões**
Torres T, et al. *Levels of Physical Activity in Patients with Severe Psoriasis: A Cross-Sectional Questionnaire Study.* Am J Clin Dermatol. 2014;15:129-35.	· Diminuição dos níveis de actividade física na psoríase; · Provável influência no risco de doença cardiovascular nos doentes com psoríase.
Torres T, *et al. Framingham Risk Score underestimates cardiovascular disease risk in severe psoriatic patients: Implications in cardiovascular risk factors management and primary prevention of cardiovascular disease*. J Dermatol. 2013;40:923-6.	· Elevado subdiagnóstico e subtratamento dos FRCV nos doentes com psoríase; · Actuais recomendações para o tratamento dos FRCV e prevenção de doença cardiovascular desajustadas à população psoriática.
MARCADORES DE RISCO CARDIOVASCULARES EM DOENTES COM PSORÍASE	
Publicação	**Resultados/Conclusões**
Cabete J*, Torres T*, *et al. Erectile dysfunction in psoriasis patients.* Eur J Dermatol. 2014	· Aumento da prevalência e gravidade de disfunção eréctil nos doentes com psoríase; · Psoríase como provável factor de risco independente de disfunção eréctil; · Disfunção eréctil como marcador precoce de doença cardiovascular na psoríase.
Torres T, *et al. Complement C3 as a marker of cardiometabolic risk in psoriasis*. Arch Dermatol Res. 2014 May 22.	· Aumento dos níveis séricos de C3 na psoríase; · C3 como marcador de risco cardiometabólico na psoríase.
Torres T, *et al. Epicardial adipose tissue and coronary artery calcification in psoriasis patients.* J Eur Acad Dermatol Venereol. 2014 Apr 21.	· Aumento do volume de gordura epicárdica, independentemente da gordura visceral abdominal, nos doentes com psoríase; · Gordura epicárdica como preditor independente de aterosclerose coronária em doentes com psoríase.
INFLUÊNCIA DE FACTORES GENÉTICOS NO DESENVOLVIMENTO DE DOENÇA CARDIOVASCULAR NA PSORÍASE	
Publicação	**Resultados/Conclusões**
Torres T, *et al. Cardiovascular comorbidities in childhood psoriasis.* Eur J Dermatol. 2014;24:229-35.	· Aumento da prevalência de adiposidade excessiva e de dois componentes do síndrome metabólico em crianças com psoríase; · Risco cardiovascular nos doentes com psoríase poderá ser, em parte, geneticamente determinado.
Torres T, *et al. Influence of IL-6 gene polymorphisms in epicardial adipose tissue and coronary artery calcification in psoriasis patients*. Br J Dermatol. 2014	· Associação entre a presença do alelo G do polimorfismo rs2069840 [-1753C/G] do gene da IL-6 e o aumento do volume de gordura epicárdica, independentemente da gordura visceral abdominal.
Torres T, *et al. Influence of TNF-α gene polymorphisms in coronary artery calcification in psoriasis patients.* J Eur Acad Dermatol Venereol. 2014.	· Ø associação entre os polimorfismos genéticos do TNF-α estudados e a presença de CAC.
Torres T, *et al. Lack of association between leptin, leptin receptor and adiponectin gene polymorphisms and epicardial adipose tissue, abdominal visceral fat and atherosclerotic burden in psoriasis patients.*	· Ø associação entre os polimorfismos genéticos da leptina, receptor da leptina e adiponectina estudados e a presença de CAC e o aumento do volume de gordura epicárdica e gordura visceral abdominal.

CONCLUSÃO

A investigação desenvolvida nos últimos anos afastou definitivamente o conceito da psoríase como uma doença exclusivamente cutânea. Actualmente a psoríase é considerada uma doença inflamatória sistémica, associada a múltiplas comorbilidades, cujo impacto no prognóstico, especialmente na morbilidade e mortalidade cardiovascular, é amplamente reconhecido. Nos últimos anos, o impacto na qualidade de vida dos doentes e a dificuldade do tratamento das lesões cutâneas foram ultrapassados com os avanços observados na terapêutica. No entanto, o conhecimento da associação entre psoríase, comorbilidades e doença cardiovascular é ainda escasso. É essencial alterar o paradigma da abordagem da psoríase, que deverá deixar de estar centrada no tratamento das lesões cutâneas e passar a compreender todas as patologias associadas à doença. De facto, uma abordagem optimizada do risco de doença cardiovascular nos doentes com psoríase poderá resultar numa melhoria significativa do prognóstico destes doentes. Para isso, é essencial entender os factores e mecanismos que estão envolvidos nesta associação.

Esta investigação permitiu minorar a lacuna de conhecimento nesta área. Demonstrámos que o risco de doença cardiovascular nos doentes com psoríase é influenciado, não só por factores intrínsecos à doença, mas também por outros externos, susceptíveis de correcção, como a actividade física, ou uma melhoria na abordagem dos FRCV e prevenção de doença cardiovascular.

Identificaram-se, também, marcadores de risco, laboratoriais e clínicos, passíveis de utilização na prática clínica, que permitam o reconhecimento de doentes psoriáticos em maior risco de desenvolver doença cardiovascular.

Por fim, este trabalho contribuiu para aumentar a evidência de que o risco cardiovascular na psoríase é, pelo menos em parte, geneticamente determinado. Demonstrámos que em idade pediátrica os resultados são semelhantes aos

observados na população adulta e que poderão existir marcadores genéticos, envolvendo o gene da IL-6, responsáveis pelo aumento do volume de gordura epicárdica nos doentes com psoríase. A utilização de biomarcadores genéticos tem sido crescente em todas as áreas da medicina, para prever o início ou a recorrência de certas patologias e para individualizar/personalizar a abordagem dos doentes. Provavelmente, num futuro próximo, será possível reconhecer precocemente os doentes de risco e assim avançar para uma medicina personalizada.

Assim, as implicações clínicas desta investigação poderão ser inúmeras e relevantes. Com identificação de doentes em maior risco será possível, implementar medidas preventivas, estimular a adopção de comportamentos saudáveis e tratar de forma mais agressiva os diferentes FRCV nesses doentes.

Também a sensibilização, não só dos dermatologistas, mas também de todos os médicos que observam doentes psoriáticos, de que os doentes com psoríase são uma população de risco, em que é essencial o diagnóstico e tratamento dos FRCV, é fundamental. Uma das estratégias poderá passar pela publicação de artigos científicos em revistas médicas generalistas ou de outras especialidades informando e alertando para esta realidade. (Torres T, *et al. Psoriasis and cardiovascular disease.* Acta Med Port. 2013 Sep-Oct;26(5):601-7; Torres T, *et al. Psoriasis: The visible killer*. Rev Port Cardiol. 2014 Feb;33(2):95-9). Também a organização hospitalar deverá reflectir esta preocupação, implementando consultas multidisciplinares.

CAPÍTULO 4: PERSPECTIVAS FUTURAS

PERSPETIVAS FUTURAS

Os progressos observados nos últimos anos no conhecimento da psoríase foram extraordinários. A complexa fisiopatogenia da psoríase foi sendo esclarecida aos poucos, permitindo o desenvolvimento de novos fármacos, cada vez mais selectivos, que revolucionaram o tratamento da doença. Ao mesmo tempo, confirmou-se que a psoríase não é uma doença exclusivamente cutânea, mas que se associa a múltiplas comorbilidades, com natural impacto na qualidade de vida, morbilidade e mortalidade dos doentes. Em nenhuma outra área da dermatologia se observaram tais avanços e, principalmente, com o impacto que estes tiveram na melhoria da abordagem e tratamento dos doentes com psoríase.

Contudo, existe ainda nesta área um longo percurso a percorrer para entender completamente todos os mecanismos que expliquem a associação entre psoríase, aterosclerose e comorbilidades cardiometabólicas.

Os resultados apresentados nesta tese permitiram avançar um pouco mais no conhecimento desta área, no entanto muitas questões estão ainda por responder. Será essencial continuar a procurar biomarcadores que permitam identificar os doentes de maior risco cardiovascular, identificar outros mecanismos fisiopatológicos passíveis de intervenção terapêutica e perceber o efeito do tratamento sistémico precoce no prognóstico cardiovascular destes doentes.

Por isso, durante a realização deste projecto, surgiram planos de investigação futura, nos quais já iniciamos o nosso envolvimento:

1. Avaliação do desequilíbrio entre as células Th17 e as células T reguladoras na psoríase e sua influência no desenvolvimento de aterosclerose.

O desequilíbrio Th17/Treg foi descrito na psoríase e na aterosclerose. Em breve, estarão disponíveis agentes biológicos para o tratamento da psoríase direccionados à via Th17/IL-17, pelo que será relevante entender o papel deste

desequilíbrio na associação psoríase/aterosclerose e se estes agentes poderão ter impacto em ambas as doenças.

2. Avaliação das comorbilidades cardiometabólicas e risco cardiovascular na psoríase, artrite reumatóide e espondilite anquilosante.

As doenças imunomediadas, como a artrite reumatóide e a espondilite anquilosante, também têm sido associadas a um maior risco de doença cardiovascular. No entanto, o perfil de comorbilidades parece diferir do da psoríase. Na psoríase, a obesidade tem um papel central e relevante, enquanto a inflamação sistémica parece ser o principal factor de risco na artrite reumatóide. Estas diferenças têm certamente implicações clínicas e terapêuticas na abordagem destes doentes. Até ao momento, os estudos conduzidos neste tópico são escassos, pelo que nos parece uma área interessante de investigação.

3. Avaliação do impacto do tratamento da psoríase na diminuição do risco de doença cardiovascular

Vários estudos apontam para um efeito positivo do tratamento com inibidores do TNF-α no risco cardiovascular dos doentes com doenças reumatológicas assim como com psoríase. Contudo é importante avaliar se o tratamento com outros agentes, biológicos, sistémicos convencionais e fototerapia têm o mesmo resultado.

O fascinante da ciência é que quanto mais avançamos e mais respostas vamos encontrando, mais dúvidas nos surgem e mais portas se abrem, estimulando a vontade de prosseguir uma caminhada que, felizmente, nunca terá um fim.

CAPÍTULO 5: BIBLIOGRAFIA

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